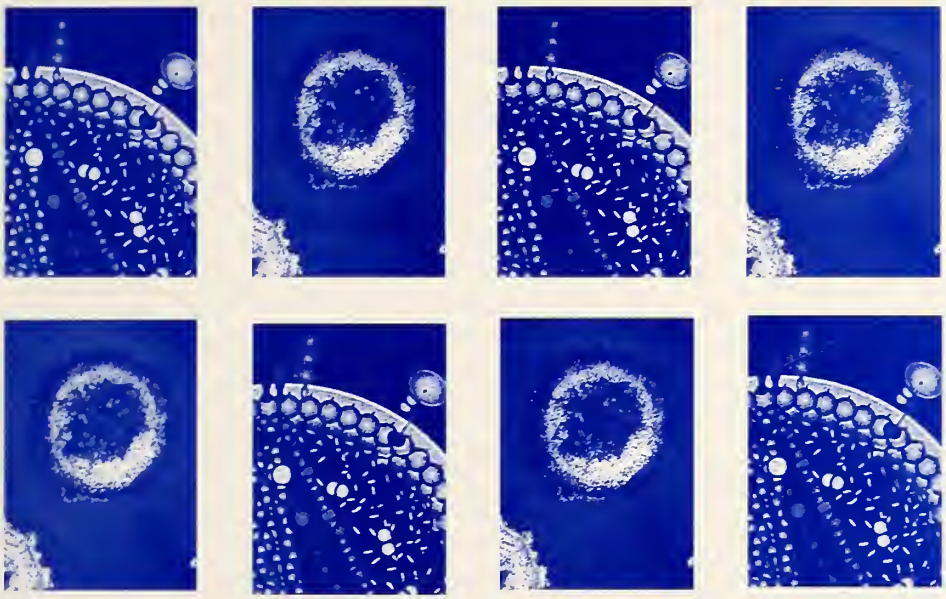

National Institutes of Health
Fiscal Year 1999
Plan for HIV-Related Research

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

National Institutes of Health
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Prepared by the NIH Office of AIDS Research

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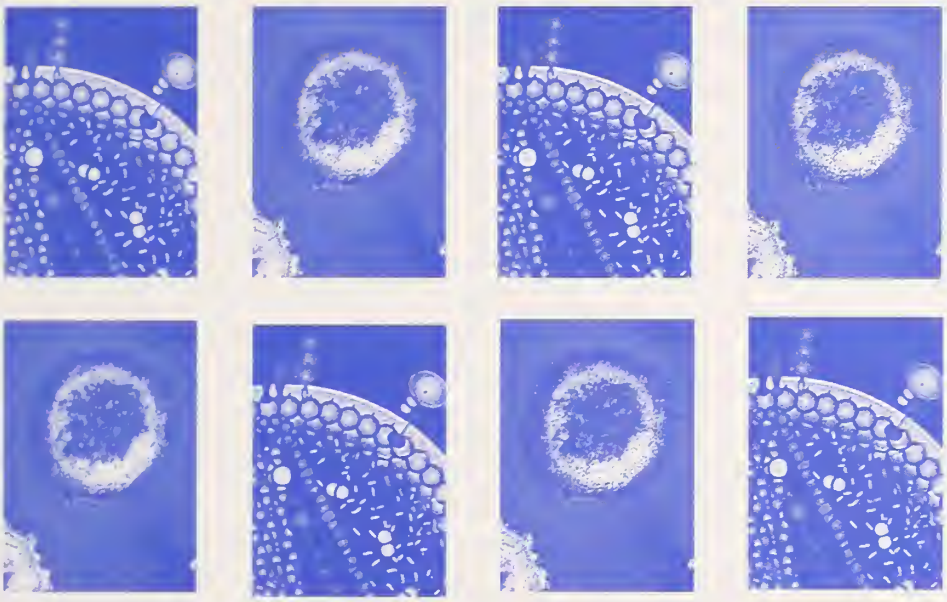


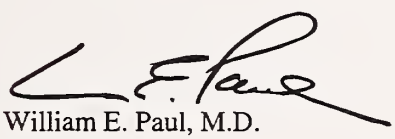
Foreword

As the Director of the Office of AIDS Research, I am pleased to present the National Institutes of Health FY 1999 Plan for HIV-Related Research. The development of this comprehensive plan represents a collaborative effort among hundreds of individuals—NIH Institute Directors; NIH scientists and program staff; non-Government experts, including scientists from academia, foundations, and industry; and AIDS community representatives. To each of them, I express my deep appreciation.

This plan reflects and addresses the recommendations set forth in the "Levine Report," the comprehensive evaluation of the NIH AIDS research program. The evaluation process involved an intensive outside review of NIH by more than 100 scientific experts and community representatives and a deliberative and comprehensive implementation of their recommendations. Thus this plan represents a true merging of the planning and evaluation processes.

The plan serves not only as the framework on which the development of the budget is based, but also as a way to determine the use of AIDS-designated dollars and for tracking and monitoring those expenditures. The plan defines those research areas for which AIDS-designated funds may be allocated.

Because of the legislative authorities provided to OAR for planning and budgeting for AIDS research, it has been possible to set new scientific priorities and to reshape and restructure the research enterprise toward our goal of preventing and curing AIDS. The Nation has invested major resources in the NIH AIDS research program. I believe that the steps taken by OAR over the past few years, resulting in this Plan, have allowed us to demonstrate that the Nation's investment is indeed well spent.



William E. Paul, M.D.
Director
Office of AIDS Research

Legislative Mandate

The National Institutes of Health (NIH) Revitalization Act of 1993 (Public Law 103-43) strengthened the Office of AIDS Research (OAR) and provided that the Director of the OAR "shall plan, coordinate and evaluate research and other activities conducted or supported" by NIH. The Director of OAR "shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health" and shall "establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health...; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities...; and ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan."

The law further provides that "the Director of the Office shall ensure that the plan provides for basic research; provides for applied research; provides for research that is conducted by the agencies; provides for research that is supported by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social sciences research."

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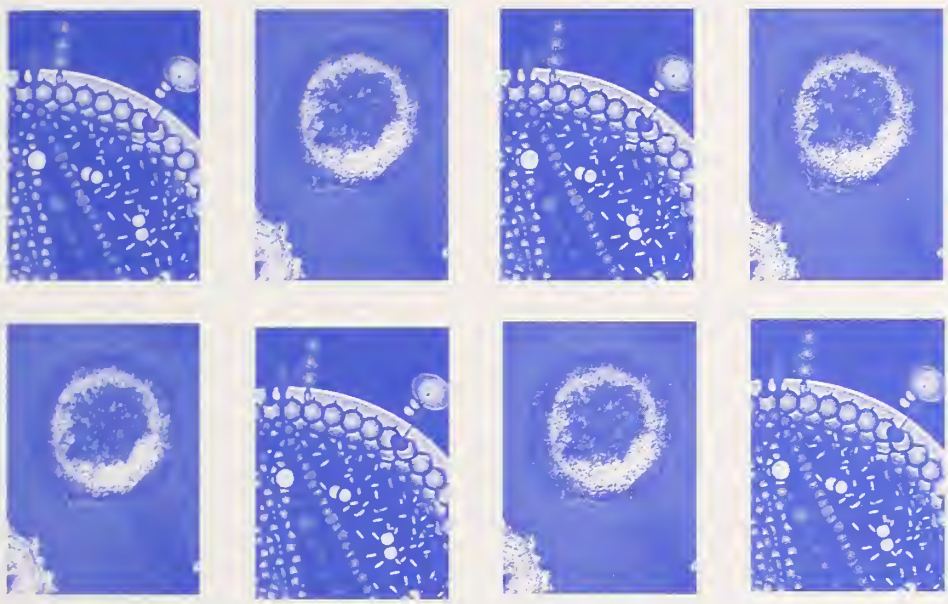

NIH HIV-Related Research Program

NIH HIV-Related Research Program

Implementing the Levine Report

In late 1994, it became clear that AIDS research had reached a turning point and new priorities and directions for the future were necessary. A unique process was initiated: The NIH AIDS Research Program Evaluation Task Force, a panel of more than 100 distinguished scientists and experts from the United States and around the world, chaired by Dr. Arnold Levine of Princeton University, was formed by the Office of AIDS Research Advisory Council (OARAC). The Task Force was asked to conduct a comprehensive evaluation of the entire NIH AIDS research program. This review was unprecedented because of the magnitude of the AIDS research program, which cuts across every NIH Institute and Center. The group was asked to assess whether the program as a whole was moving effectively and efficiently toward the goal of preventing and curing AIDS.

Six Area Review Panels reviewed AIDS research in the following areas: Etiology and Pathogenesis; Drug Discovery; Clinical Trials; Vaccine Research and Development; Behavioral, Social Science, and Prevention Research; and Natural History, Epidemiology, and Prevention Research. *Ad hoc* groups examined opportunistic infections, animal models, alternative and complementary therapies, training programs, and AIDS research centers. The entire Report of the NIH AIDS Research Program Task Force, commonly known as the "Levine Report," is available on the OAR website of the Internet at http://www.nih.gov/od/oar/.

This landmark report assessed all NIH-sponsored AIDS research to determine whether the most promising areas of science were being supported, the critical scientific questions were being addressed, and the most effective use was being made of Federal AIDS research resources. It provided a blueprint for restructuring the NIH AIDS research program to streamline research, strengthen high-quality programs, eliminate inadequate programs, and ensure that the American people reap the full benefits of their substantial investment in AIDS research.

Most importantly, that blueprint is becoming a reality. The report has had a significant effect on almost every aspect of the AIDS research program—in setting the scientific agenda, refocusing priorities, and shaping the AIDS research budget. The recommendations helped frame OAR's final distribution of the FY 1997 appropriation, the FY 1998 research plan and budget request, and this FY 1999 research plan. It is anticipated that the priorities established by these recommendations will have an impact not only on Government-supported

research but on the research agendas of industry and private research organizations both in the United States and abroad.

The report has had a profound impact in helping to establish the appropriate balance in the AIDS research program in two critical areas: (1) between investigator-initiated research grants and targeted, directed science and (2) between research to develop treatments and an eventual cure for those who are already infected and research to prevent infection.

Before embarking on the evaluation process, OAR already had identified the need to place greater emphasis on investigator-initiated science and to increase the proportion of funding devoted to basic research. The Levine Report confirmed these priorities. Between FY 1994 and the FY 1998 President's budget request, OAR has increased the number of research grants by 50 percent, thus encouraging innovation from a wider group of investigators.

Perhaps the most significant recommendations of the report relate to vaccine research. The changes that have been implemented in this area have enormous potential significance not only for AIDS but for other diseases as well. The report recognized that only a truly effective preventive vaccine can limit and eventually eliminate the threat of AIDS. The reviewers placed high priority on the need to restructure and reinvigorate the AIDS vaccine program with leadership and guidance from eminent non-Government scientists.

NIH has taken a number of steps to carry out this critical recommendation. Nobel laureate Dr. David Baltimore was recruited to lead this reinvigorated effort, and he has assembled a group of outstanding scientists to serve with him on the AIDS Vaccine Research Committee (AVRC). Their charge is to energize the development of new strategies toward the discovery and development of a safe and effective AIDS vaccine. To facilitate this effort, OAR has made a major financial investment in AIDS vaccine research. The FY 1998 President's budget request represented a 33.6-percent increase for vaccine research in the 2-year period since FY 1996, a sign of our commitment to this effort. It is anticipated that funding will be further increased with the final FY 1998 Congressional appropriation and in the FY 1999 President's budget request. The President also emphasized the importance of AIDS vaccine research both in his State of the Union address and in a commencement speech in May 1997 at Morgan State University. At that time he also announced another important NIH vaccine initiative, the establishment of a joint National Institute of Allergy and Infectious Diseases (NIAID)/National Cancer Institute (NCI) intramural Vaccine Research Center. Progress made in the development of an AIDS vaccine will certainly have implications for vaccines against other life-threatening illnesses.

The Levine Report also urged NIH to develop a Prevention Science Agenda, combining behavioral research and biomedical interventions such as topical microbicides, female-controlled barriers,

methods to prevent mother-to-child transmission, and prevention and treatment of sexually transmitted diseases (STDs). OAR convened a group of experts to assist in identifying the most promising areas for additional investment, which are incorporated in this plan.

The Levine Report determined that the ability of NIH to manage and categorize AIDS research spending would be facilitated by a clear operational definition of AIDS and AIDS-related research, which should evolve in response to scientific priorities and opportunities. Only those projects meeting the definition should be supported with AIDS-designated funds. Beginning with this document, NIH will use the annual Plan for HIV-Related Research as the formal definition of what constitutes AIDS research. The ICDs (Institutes, Centers, and Divisions) will use this definition in coding and reporting their AIDS-related programs and projects. Each objective in the plan is assigned a code. All research projects funded with AIDS-designated dollars are coded by the funding institute to the appropriate scientific objective(s) in the plan, and the project is entered in the AIDS Research Information System (ARIS) database.

Progress Against AIDS

A number of new and exciting research advances provide optimism and open new areas for investigation. Protease inhibitors, a new class of drugs, used in combination with other antiretroviral therapies, have been shown to remarkably diminish the amount of HIV in an infected individual. Receptors for molecules called chemokines have been identified as critical cofactors for HIV infection, providing us with an entirely new set of targets for anti-HIV therapies and new approaches for vaccine development. But it is essential to point out that the news, while good, cannot lead to complacency. The end of this pandemic is not in sight. The new drugs, while promising, are not a panacea. We do not know how long the benefits of the drugs will last. It is far from clear that immune function of treated individuals can be restored without additional interventions. There are many for whom the new drug regimens have not been effective or for whom the side-effects are not tolerable. The challenge now is to develop more effective drugs and to prepare for the possible emergence of drug-resistant strains of the virus.

The sobering fact is that we have made little progress against the devastating spread of the epidemic around the globe. AIDS is the number one cause of death among young adults in the United States. Rates of increase in AIDS cases in the U.S. are greatest for women, adolescents, persons infected through heterosexual contact, minorities, and injecting drug users (IDUs). More than 29 million people worldwide have been infected with HIV, with more than 3 million new infections in just the past year. The majority of these infections occurs in the poorest parts of the world, in countries without the resources or the health care systems to benefit from the new anti-

HIV drugs. AIDS has brought about a significant decline in overall life expectancy in many African countries, threatening the economies of these already-poor nations and robbing them of their workforce. A safe and effective AIDS vaccine is an urgent global public health imperative. Without a vaccine, AIDS will soon overtake tuberculosis (TB) as the leading infectious cause of death in the world.

Impact of AIDS Research

The Nation's investment in HIV-related research is providing major benefits in our ability to understand and treat a wide spectrum of other infectious, malignant, neurologic, autoimmune, and metabolic diseases. Basic knowledge of the biology of HIV infection and the processes by which it causes AIDS benefits other areas of basic research including immunology, virology, microbiology, molecular biology, and genetics. Knowledge gained from the study of drugs to treat HIV infection and its complications also has helped establish new approaches for the design and conduct of more rapid clinical studies, as well as those that address the special recruitment requirements of women, minorities, and other underserved populations.

Effective drugs to treat other infectious diseases

The successful development of two classes of drugs that limit the replication of HIV, reverse transcriptase (RT) inhibitors and protease inhibitors, represents a landmark in drug development for the control of viral diseases. As a result, AIDS research has provided a new paradigm for confronting viral diseases in general. Prior to the development of these potent drugs, virtually all efforts to deal with viral diseases involved prevention (using vaccines) or palliation (treating symptoms). Few effective treatments were available for most common viral infections. The AIDS drug development experience not only benefits development of treatments for other viral diseases but will also hasten drug development efforts for bacterial, mycobacterial, and fungal diseases.

- The drug lamivudine (also known as 3TC), initially developed to treat HIV infection, now has been shown to be the most effective therapy for chronic hepatitis B infection. Prior to its availability, no effective therapies existed, and many infected persons would proceed inexorably to cirrhosis, liver failure, and liver cancer. Lamivudine represents a "lead compound" that should expedite the development of even more effective agents to treat, and perhaps even cure, chronic hepatitis B infections.

- Experience gained in the course of HIV drug development is being applied to potential therapies for hepatitis C, influenza, and cytomegalovirus (CMV) infection.

- New animal models developed in the course of AIDS research will facilitate studies of other infectious diseases.

Advances in methods for drug design

AIDS therapeutic research has demonstrated the importance of rational drug design and has resulted in a new generation of powerful inhibitors of HIV replication. Progress in this area depends on the identification of a promising molecular target for drug therapy, determination of the three-dimensional structure of the target molecule using sophisticated X-ray crystallographic methods, and structure-based drug design aided by the techniques of structural biology and computer-based molecular modeling. HIV research has benefited from the availability of these individual methods and has fostered significant improvements in each of these critical technologies, including X-ray crystallographic methodologies, nuclear magnetic resonance techniques, and computational approaches to chemical processes. These advances will continue to benefit efforts to develop new drugs for other diseases.

Treatments for opportunistic infections

Individuals who receive drugs that intentionally or unintentionally suppress the function of the immune system are, like AIDS patients, at significantly increased risk of opportunistic infections (OIs). Many forms of modern treatment for cancer involve the use of drugs that suppress the immune system. Transplantation of solid organs as treatment for organ failure (e.g., heart, liver, or kidney failure) and bone marrow transplants to treat malignant (e.g., leukemia) or hematologic diseases (e.g., immunodeficiency syndromes or genetic disorders of hemoglobin production such as sickle cell anemia) necessarily involve the use of drugs that suppress the immune system to prevent rejection of the transplanted organs or tissues. The development of effective drugs to prevent and treat many of the microorganisms that cause OIs promises real benefit to those undergoing cancer chemotherapy or receiving antitransplant rejection therapy.

- Clinical research to delay or prevent life-threatening AIDS-related OIs has stimulated the development of effective drugs to treat these pathogens, such as *Pneumocystis carinii*, CMV (a cause of blindness in people with AIDS and life-threatening pneumonias and serious gastrointestinal infections in bone marrow and organ transplant recipients), and a variety of serious fungal infections that cause meningitis or disseminated infections in immunosuppressed persons.

- AIDS research has helped establish the concept of "prophylaxis" of certain infections in immunosuppressed persons. Providing regular, low doses of drugs that are intended to prevent development of disease decreases the risk of OIs. This approach is now standard practice to prevent infections caused by a variety of viruses (such as CMV), fungi, and mycobacteria in immunosuppressed patients.

Understanding the origins and manifestations of malignancies

One of the cardinal manifestations of AIDS is the predisposition to develop specific types of cancer, including Kaposi's sarcoma (KS) and non-Hodgkin's lymphomas. That these cancers arise in the setting of host immunodeficiency provides strong support for the notion that the immune system can play an important role in suppressing the development of cancers. HIV infection provides a unique model to study the role of the immune system in the emergence of cancers and to test novel approaches by which immune responses can be modified to help treat established malignancies.

- The discovery of the likely cause of KS, HHV-8 (human herpesvirus-8), provides a model for using novel techniques of molecular biology to search for infectious cancer-causing agents in any type of cancer. Studies involving HIV-infected persons now serve as the model to identify potential infectious etiologies for a wide variety of common malignancies.

- HIV-infected women who are also infected with human papillomavirus (HPV) are at increased risk of developing cervical cancer, suggesting that the immune system also plays an important role in controlling this disease. A link between HPV infection and cervical cancer is also seen in women not infected with HIV. Study of HIV-associated cervical cancer has stimulated new areas of research and therapeutic strategies to treat this disease, which will likely benefit all women at risk of cervical cancer.

- Wasting, the intractable loss of weight, is a common clinical manifestation of both cancer and advanced HIV disease. New therapies developed to treat HIV-associated wasting, such as growth hormone treatment, may prove beneficial to persons with cancer. New anti-HIV treatments that effectively inhibit HIV replication seem to reverse the process of AIDS-associated wasting, providing an opportunity to understand how this disease manifestation arises. The results of these studies may also be of relevance to understanding the process of cancer-associated wasting.

Advances in the ability to diagnose infection and monitor the efficacy of therapy

HIV research has provided new paradigms for the diagnosis of infectious diseases and for monitoring the efficacy of therapy. Molecular diagnostic methods use sensitive techniques to detect and quantify the pathogen in an infected patient. These methods now permit more rapid diagnosis of infectious diseases, facilitate earlier introduction of effective, potentially life-saving therapies, permit the design of faster, more informative clinical trials, and allow the individualization of optimal therapies.

- Among these new technologies is the polymerase chain reaction (PCR) test used to diagnose HIV infection or the so-called viral load assays used to assess

disease progression and the efficacy of anti-HIV therapies. The development of these approaches and their validation in the course of AIDS investigations have helped speed the process of clinical evaluation of candidate AIDS therapies, and similar approaches are now being employed to study treatments for other infectious diseases. PCR-based tests are now routinely used to rapidly diagnose a number of important infectious diseases including tuberculosis, chlamydia, Lyme disease, and a variety of fungal infections.

- The development of tests to screen blood donations for the presence of HIV infection has stimulated advances in technologies that could be used to screen blood for the presence of other important infectious diseases, such as hepatitis C virus and HTLV-I and -II (human T lymphotropic virus), viruses that are associated with the development of leukemia and serious neurologic diseases. As a result, the safety of the blood supply has been substantially improved.

Insight into the function of the human immune system in health and disease

The investment in AIDS research has enormously speeded the development of our understanding of the human immune system. Research on AIDS has led to major advances in our understanding of and ability to manipulate human immune responses. This should allow more effective approaches to treat diseases in which dysregulated immune responses are either the actual cause of, or substantial contributing factors to, the fundamental disease process, including allergies, multiple sclerosis, juvenile diabetes, rheumatoid arthritis, and systemic lupus erythematosus.

Promising immunologic approaches currently being investigated to control cancer include the use of cytokine therapy to boost antitumor immune responses, the use of genetically modified tumor cells that express cytokines or other gene products intended to redirect host immune responses to more effectively fight the resident tumor cell burden, and the expansion (in tissue culture) and transfer of immune cells that can recognize and kill tumor cells. Similar approaches have been actively pursued in the course of research on HIV therapies, and experience from studies in HIV-infected persons has helped accelerate the development and testing of these treatments in the context of cancer therapy.

New approaches to the design and conduct of drug trials

The national HIV research effort has brought about unprecedented cooperation among Federal, university, and pharmaceutical industry scientists in the development of potential therapeutic agents and vaccines. HIV research has resulted in new approaches for designing and conducting clinical trials and for recruiting and enrolling patients, especially women, children, and minorities in these studies.

These models are now being applied to test treatments for other diseases in faster, more efficient, and more inclusive ways.

- New approaches for conducting clinical trials have been developed, including community-based trials, which capture the expertise of community physicians. AIDS clinical trials have demonstrated the importance of providing ancillary services, such as general health care, transportation, obstetrical care, day care for children, and other related services, to recruit and ensure the continued participation of women, children, adolescents, and minorities in clinical trials.

- AIDS clinical trials pioneered the development of community advisory boards (CABs) to assist clinical trial sites in ensuring close cooperation with community constituency groups (CCGs). Such strategies will be applied in the study of treatments for other diseases in the future.

- The "parallel-track" mechanism has been shown to be consistent with the conduct of effective clinical studies of candidate therapies and will benefit persons suffering from all types of life-threatening diseases. This mechanism permits access to promising drug treatments prior to their formal approval by the Food and Drug Administration (FDA) for individuals who would not otherwise qualify for participation in specific clinical studies.

Advances in the study of neurologic manifestations

Research aimed at understanding how HIV enters the central nervous system (CNS) and how it results in neurologic disease has yielded important knowledge regarding the role that inflammatory processes within the CNS can have in neuronal degeneration and impairment of cognitive and motor functions. Studies on the mechanisms involved when HIV crosses the blood–brain barrier to infect cells within the brain and how drug therapies can be delivered more effectively to the brain have led to a better understanding of the mechanisms through which this barrier functions and how it may be circumvented. The results of this research have important implications for research on Alzheimer's disease, dementia, multiple sclerosis, neuropsychological disorders, encephalitis, and meningitis.

Expansion of basic science knowledge base

The investment in AIDS and HIV research has enormously speeded our progress in many areas of basic science, including those directly impinging upon the biotechnology industry. Indeed, this effort has been a major contributor to the knowledge base upon which the biotechnology industry has been built. Biotechnology companies are capitalizing on the new basic biomedical information provided by HIV research, most notably new findings regarding chemokines and novel proteins as targets for drug and vaccine development.

Insights into the impact of human behavior on public health

Behavioral and social sciences research on HIV infection and AIDS has demonstrated the important interaction of biological, psychological, and social factors as contributors to disease prevention, transmission, and progression among individuals and population groups. Lessons learned from these studies have improved our ability to study human behaviors that affect disease risk and to develop effective methods to encourage behavior change.

Progress in understanding "emerging" and reemerging infectious diseases

The emergence of HIV infection, Ebola virus infection, and hantavirus infection within the past 15 years has demonstrated not only that new diseases can appear in human populations, but that they are also likely to continue to emerge in the future. Diseases once deemed under control also have reemerged as important health problems in this country and around the world. Studies of the origin of HIV infection and the processes that contributed to its worldwide spread have significant implications for preventing or limiting similar epidemics in the future.

- HIV infection in humans appears to have originated from a virus present in certain nonhuman primates. Inadvertent transmission of the virus across species (so-called zoonotic infection) allowed the virus to enter human populations. Study of the origins and spread of HIV infection will provide a better understanding of how this process occurs and how it can be prevented.

- Studies of HIV-infected individuals with clinical syndromes of previously unknown etiology have led to the discovery of a number of important new infectious agents including HHV-6, the cause of a number of clinical illnesses including exanthem subitum in children; HHV-7, not yet associated with a specific clinical illness; HHV-8 or KSHV, the likely causative agent of KS; bacteria of the genus rochalimaea, also known as Bartonella, the causative agent of bacillary angiomatosis and "cat scratch fever"; and a variety of previously uncharacterized fungi. The discovery of these agents and diagnostic methods to detect them also led to their identification in persons not infected with HIV. HHV-6, for example, causes serious clinical complications in persons not infected with HIV.

- Using molecular diagnostic techniques developed in the study of the AIDS epidemic, Centers for Disease Control and Prevention (CDC) researchers rapidly identified hantavirus as the causative virus infection of an outbreak of cases of fatal pneumonia in the southwestern United States a few years ago. These techniques allowed the researchers to determine the origin of the virus in local populations of mice and to limit the spread of infection.

- The development of international collaborations for tracking the natural history and epidemiology of infectious diseases and for obtaining and identifying variants of infectious agents from different geographic regions helped expedite research on AIDS. This experience and the collaborations established will be of great value should new epidemic diseases emerge in the future.

- Computational methods and mathematical modeling developed to study HIV transmission now are being applied to track the parameters of transmission and dissemination of the bovine spongiform encephalopathy agent and will certainly benefit the study of other infectious agents as well.

Office of AIDS Research

OAR was established in 1988 by the Director of NIH and the Department of Health and Human Services (DHHS) Assistant Secretary of Health. The primary responsibility of OAR was to coordinate the AIDS research effort across NIH and serve as a focal point for AIDS policy and budget development within the Office of the Director, NIH. The NIH Reauthorization Act of 1993 gave broad new authorities to the office. OAR is responsible for the development of the annual comprehensive planning and budgeting process for all NIH AIDS research and for preparation of a Presidential bypass budget. The law also requires OAR to evaluate the AIDS activities of each of the ICDs as well as provide for the periodic reevaluation of such activities. OAR maintains a discretionary fund, and the appropriations committees have provided OAR with transfer authority permitting it to move up to 3 percent of funds between Institutes.

OAR has established and supports the efforts of six trans-NIH Coordinating Committees in the following areas: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral and Social Science Research, and Information Dissemination. The Committees represent those Institutes with the most significant research portfolios in these areas; members were nominated by the ICDs. The committees foster collaboration and coordination and assist in the development of the NIH plan and budget for AIDS research.

To carry out its activities, OAR depends upon the expert advice of OARAC, its advisory council, which is composed of non-Government experts from a broad array of disciplines as well as AIDS community representatives. The Advisory Council reviews the annual plan, budget requests, and discretionary fund disbursements. OAR supports the Intramural AIDS Targeted Antiviral Program (IATAP) and the NIH AIDS Research Loan Repayment Program (LRP). OAR supports a number of initiatives to promote the distribution of research information to researchers, physicians, institutions, and communities. OAR also monitors and fosters plans for

NIH involvement in international AIDS research activities and provides financial assistance to allow participants from developing countries to attend AIDS conferences.

NIH Institute and Center Support of HIV/AIDS Research

Each NIH Institute and Center (IC) is involved in some HIV/AIDS-related research activity, consistent with its individual mission. The ICs whose research programs are most heavily concerned with HIV, AIDS, and their sequelae are NIAID, NCI, the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), the National Center for Research Resources (NCRR), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Child Health and Human Development (NICHD). The Warren Grant Magnuson Clinical Center provides the infrastructure for intramural clinical studies sponsored by the ICs.

Development of the FY 1999 Plan

The planning process instituted by OAR is a unique and inclusive one, inviting the participation of scientific experts from academia, Government, industry, and foundations, as well as AIDS community representatives. Through this process, a consensus is developed regarding the direction and priorities for AIDS research.

The six OAR Coordinating Committees prepare the first draft of the plan for their specific areas of AIDS/HIV research: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral and Social Sciences Research, and Information Dissemination. Each group also addresses training needs in these areas. The Coordinating Committees developed the first draft of the FY 1999 Plan through a series of meetings, using the FY 1998 NIH Plan for HIV-Related Research; the Report of the NIH AIDS Research Program Evaluation Task Force (the Levine Report); and the NIH Plan to Implement Recommendations of the NIH AIDS Research Evaluation Task Force for their framework. The draft plan developed by the Coordinating Committees was then sent to each ICD Director and ICD AIDS Coordinator for their recommendations and suggested additions or changes.

To achieve the broadest possible consensus regarding the plan, OAR sponsored a 2-day workshop to seek the input of non-NIH experts, including scientists from academia, foundations, and industry, as well as community representatives. These experts were invited to review and prioritize the draft plan. The meeting was divided into four concurrent Planning Groups: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, and Behavioral and Social Sciences Research. Each group was composed of non-NIH scientists, community representatives, and NIH scientists who are members of the OAR Coordinating Committee for that area.

Members of the Prevention Sciences Working Group also participated in the workshop.

The workshop did not include a planning group for vaccine research for a very important reason. To implement the critical recommendations of the Levine Report in the area of vaccine research, NIH has empaneled the AIDS Vaccine Research Committee, chaired by Dr. David Baltimore. Because it is the mandate of this committee to provide guidance and leadership to the vaccine research programs of NIH, it was most appropriate that this group of eminent non-Government scientists review and shape the plan. Thus, the vaccine research section of the plan was reviewed separately by the "Baltimore Committee." It is anticipated that, in future years, OAR will also seek non-Government consultation on the plan through its newly established Prevention Sciences Working Group and Therapeutics Working Group.

Structure of the Plan

The plan is divided into categories representing the NIH AIDS research areas of emphasis: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral and Social Science Research; Training, Infrastructure, and Capacity Building; and Information Dissemination. The format of the plan is as follows:

- **AREA OF EMPHASIS:** The seven major areas listed above.
- **STATUS:** A brief review of current research activities and the state of knowledge within that scientific area.
- **SCIENTIFIC ISSUES:** The gaps in knowledge that must be addressed are listed in priority order.
- **OBJECTIVES:** The scientific questions to address each of the prioritized Scientific Issues.
- **STRATEGIES:** Specific scientific strategies to be addressed are not prioritized but serve to define those avenues and approaches that may be pursued within the scope of AIDS and AIDS-related research.

AIDS Research Priorities

The research objectives and priorities of this FY 1999 NIH Plan for HIV-Related Research thus reflect a broad scientific consensus including Government and non-Government experts as well as community representatives. The key priorities identified through this process are:

- A continued emphasis on fundamental science, particularly investigator-initiated research;
- A comprehensive effort, including several important new research initiatives, to develop new vaccine candidates and to bring them to clinical trial as soon as possible;
- An augmentation of research efforts to better understand the human immune system;
- An emphasis on prevention science research, including enhanced studies of risk-taking behavior and the development of strategies to avert infection, such as microbicides, female-controlled barriers, and STD treatment and prevention; and
- A vigorous therapeutic research program, emphasizing both drug discovery and an efficient clinical trials system, with additional emphasis on increased participation of women, minorities, and other underrepresented populations.

NATIONAL INSTITUTES OF HEALTH
OFFICE OF
AIDS
RESEARCH

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MAR 17 1998

TO: ICD Directors
AIDS Coordinators

FROM: Acting Director, Office of AIDS Research

SUBJECT: Fiscal Year 1999 Plan for HIV-Related Research

I am pleased to enclose a copy of the National Institutes of Health FY 1999 Plan for HIV-Related Research and to take this opportunity to extend our thanks and deep appreciation for your important contribution to this effort. As you know, the plan represents a unique collaborative process among hundreds of individuals: NIH Institute Directors, NIH scientists and program staff, non-government experts, including scientists from academia, foundations, and industry, and AIDS community representatives.

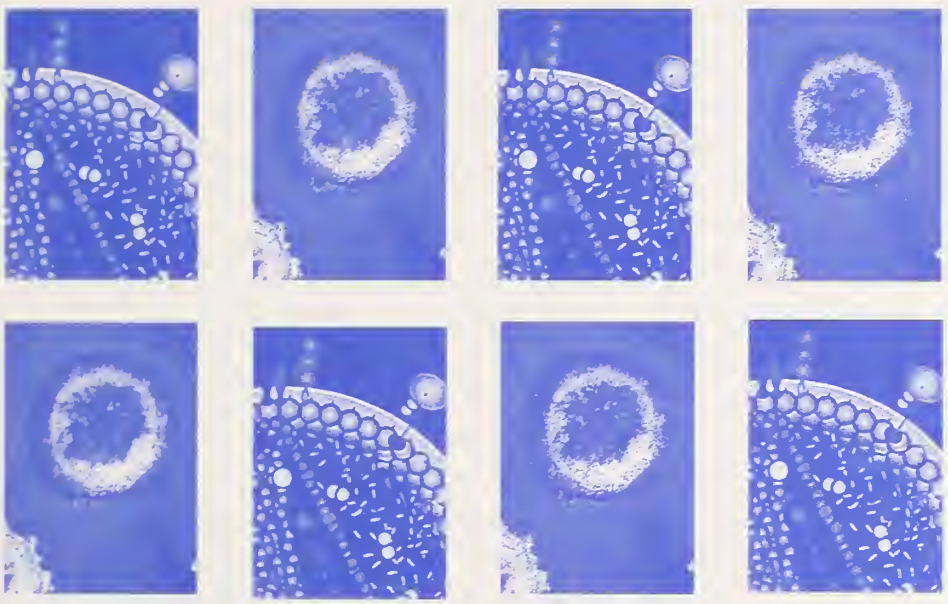
It represents collective efforts and the collective hopes of all of us that through a coordinated, well-planned, strong research program, we can break new ground and open new avenues to achieve our goal of preventing and curing AIDS.

The plan has also been posted on the Internet at www.nih.gov/od/oar. Again, our thanks for the time and energy you and your staff contributed to this planning process.

Jack Whitescarver

Jack Whitescarver, Ph.D.

Enclosure



Natural History and Epidemiology

AREA OF EMPHASIS:

Natural History and Epidemiology

Status:

Recent epidemiologic research has shown the demographics of HIV infection and AIDS in the United States shifting from an illness primarily affecting homosexual and bisexual men to the current epidemic, with increasing rates of infection in heterosexual men and women, adolescents, minorities, and drug users. NIH conducts studies to examine the transmission of HIV and the progression of HIV-related disease, including the occurrence of OIs, the development of malignancies, the incidence of neurological and neurobehavioral dysfunction, the occurrence of oral manifestations, and the development of other sequelae. Such studies examine the effects of viral factors, host factors, and other factors on the risk of infection and disease progression. Cohorts of HIV-infected individuals and HIV-uninfected individuals at risk of infection are followed in clinical epidemiology studies at domestic and international sites.

NIAID supports the HIV Network for Prevention Trials (HIVNET) in preparation for vaccine and other prevention trials of biomedical and behavioral interventions. Working in collaboration with other ICDs, this network has already begun to evaluate STD treatments, microbicides, and perinatal interventions with antiretrovirals and immunotherapy, as well as other behavioral and biomedical interventions.

International epidemiology studies supported by NIH contribute significantly to the understanding of the cellular and molecular mechanisms of HIV transmission, the progression of HIV-related disease, and the risk factors associated with HIV infection, as well as contribute to the development of new biomedical and behavioral preventive intervention strategies. NIH-sponsored natural history and epidemiology studies are investigating the transmissibility of non-B HIV clades and the reduction of HIV transmission through prevention and treatment of coexisting STDs as a means of primary HIV prevention. Another area of primary prevention research is focusing on developing new or improved means of reducing perinatal transmission in the United States and worldwide, with particular emphasis on developing methods appropriate to the developing world. The NIH-sponsored international collaborative research activities include numerous studies supported by the NCI, National Institute of Dental Research (NIDR), and Fogarty International Center (FIC). FIC training programs foster the development of research skills and infrastructure in countries where HIV infection and AIDS are epidemic, in order to facilitate biomedical and behavioral intervention trials as well as future international HIV vaccine efficacy trials.

NIH maintains repositories and databases from cohort-based studies and clinical trials. The specimens and data are made available to all qualified investigators to test specific scientific hypotheses. To ensure that repositories and databases are more widely available, NIAID and NHLBI have recently

established review mechanisms for collaborators seeking access to specific data collected from NIH-funded natural history and epidemiology, clinical trial, and behavioral AIDS-related studies. Several of the repositories maintained by NIH include the NIAID National AIDS Specimen Repository, which contains more than 1 million biological specimens linked to a database from fully characterized and longitudinally followed cohorts; the NCI Tissue and Biological Fluids Bank of HIV-Related Malignancies, which contains specimens from subjects enrolled in cross-sectional and prospective studies; the NHLBI Biological Specimen Repository, which contains more than 2 million specimens from volunteer blood donors and recipients of blood components or plasma derivatives; and the NIMH National Neurological Research Specimen Bank, which collects and distributes CNS specimens from HIV-infected donors.

The NIH investment in establishing and maintaining these unique domestic and international cohorts, repositories, and databases provides opportunities for epidemiologic and basic researchers to study unique populations, cooperatively pursue fundamental research on critical aspects of HIV transmission and disease described by intensive laboratory-based studies, and understand the dynamics of the epidemic in a population-based context. Population-based cohorts of at-risk HIV-uninfected individuals remain critical to the elucidation of the natural history of primary HIV infection.

Increases in HIV-Related Malignancies and Tuberculosis

NIH is actively supporting studies on the occurrence, natural history, and molecular epidemiology of HIV-associated preneoplastic conditions and cancers. These efforts are designed to address the significantly increased incidence and aggressiveness of cancers and preneoplastic conditions in immunodeficient individuals; e.g., increases in cancers associated with oncogenic human viruses such as non-Hodgkin's lymphoma, Hodgkin's lymphomas, KS, other multiple myelomas, and human papillomavirus-associated preneoplastic conditions and possibly cancers.

Recent data continue to implicate HHV-8 as having an important role in the development of KS, some non-Hodgkin's lymphomas, and multiple myeloma. Ongoing efforts are being focused to better understand the natural history and epidemiology of HHV-8. The importance of this and related research will increase further as the incidence of AIDS-associated malignancies are expected to increase as the life expectancy of HIV-infected patients is extended with triple-drug therapies and prophylaxis for HIV-related OIs.

The continued increase in the incidence of TB and multidrug-resistant TB related to HIV infection, both globally and in certain populations in the United States, makes this an important public health problem. NIH has responded in part to this problem by

supporting programs to address the spread of TB among IDUs. Research efforts focus on the incidence and progression of TB in HIV-infected and -uninfected active drug users and the development of improved screening and adherence strategies in order to reduce infectivity and transmission.

NIH will continue to emphasize studies on the possible impact of OIs on influencing the natural history of HIV disease, including the potential influence of such infections on HIV concentration in body fluids and tissues. The findings from these studies may be useful in identifying future opportunities to prevent disease progression and HIV transmission.

HIV Infection in Women

While many of the clinical manifestations of HIV infection in women and men are similar, HIV-infected women also experience some complications that are unique or more prevalent for them, such as vaginal and esophageal candidiasis, chronic herpes simplex infections, and cervical dysplasia. The Women's Interagency HIV Study (WIHS), a major study conducted by several NIH ICs in collaboration with other DHHS agencies, is investigating the nature and rate of disease progression in women to better characterize the clinical manifestations of HIV infection in women, determine the effects of therapeutic regimens, and identify the sociocultural and health care access factors that affect disease outcomes in women.

An important area of concern is the impact of HIV on cervical cancer. Case reports suggest that HIV-associated cases progress more rapidly and are refractory to therapy. The NCI Surveillance, Epidemiology, and End Result (SEER) program maintains a Special Surveillance Study to define more closely the incidence and spectrum of the histopathology of cervical cancer in HIV-infected women. The Multistate AIDS Cancer Match Registry also collects information relevant to this and other HIV-associated cancers. Coinfection with HPV is common in HIV-infected women, and HPV has been shown to act synergistically with HIV to increase expression of individual viral genes. The enhanced expression of viral proteins has been shown to increase viral replication, abrogate host tumor suppressor functions, and further exacerbate cellular immunodeficiency. Recent findings indicate the risk of developing cervical neoplasia is not the same with all variants of HPV-16, with certain variants conferring greater risk than others. Continued emphasis on this research area is needed.

Mother-to-Child Transmission

NIH continues to study the progression of HIV-related disease in infants and pregnant women. This research includes efforts to further characterize the timing, mechanisms, and risk factors of maternal-fetal transmission. Specific efforts of importance include those to develop improved diagnostic assays for the early detection of HIV

infection among infants, as well as assays to identify markers for predicting rapid versus slower disease progression. Another effort is ongoing to develop quantitative methods to assess viral concentration in body fluids and tissues and determine how viral concentrations affect vertical transmission and disease outcome.

In the United States, NIH is funding a large epidemiologic study evaluating factors associated with risk of perinatal transmission, as well as factors associated with maternal and infant disease progression. This study, the Women and Infants Transmission Study (WITS), cofunded by several ICs, includes extensive laboratory studies and supports a specimen repository. Another pediatric epidemiologic study is assessing cardiac and pulmonary complications among HIV-infected children. Perinatal prevention trials in the United States are conducted within the Pediatric AIDS Clinical Trials Group (PACTG).

Internationally, a wide variety of perinatal HIV prevention transmission studies are underway. These include NIAID- and NICHD-funded antiretroviral and immunotherapy trials in Africa, the Caribbean, and Thailand. In addition, NICHD, NIAID, and FIC are collaborating on several studies in Africa to determine whether micronutrient supplementation can reduce mother-to-child transmission or ameliorate disease progression in HIV-infected children. Similarly, NCI, NIAID, and FIC are collaborating on studies in Africa to determine whether vaginal and neonatal cleansing with microbicides or providing Vitamin A to pregnant women can reduce the risk of perinatal HIV transmission and to clarify the role of breast-feeding in HIV transmission.

Disease Progression

The characterization of the virologic and immunologic parameters of rapid and slow disease progression is currently underway in subsets of adult and pediatric patients in cohorts funded by several ICs. Data have shown that the amount of HIV circulating in the bloodstream is predictive of the rate of disease progression. NIAID and NCI are supporting research on individuals who (1) do not become infected despite repeated exposure to HIV, (2) appear to show clearing of the virus after initial documented infection, (3) manifest infection without immunologic progression (long-term nonprogressors), and (4) maintain stable clinical state even with prolonged immunosuppression (long-term survivors). Special focus is being placed on host genetics such as allelic heterogeneity in chemokine receptors that now are known to serve as coreceptors for HIV and on characteristics of the viral strain. Information from these cohorts will be crucial in designing and evaluating new therapeutic approaches and vaccines. Reverse transcriptase PCR technology has made quantification of HIV in plasma or serum highly reproducible, sensitive, and predictive of HIV infection. This technology likely will facilitate the elucidation of the *in vivo* natural history of HIV infection and also sexual and mother-to-child transmission.

Scientific Issue:

Despite substantial insights concerning the risk factors and modes of transmission, sizeable numbers of new HIV infections are occurring in the United States and worldwide. The development of biologically and behaviorally based interventions to interrupt transmission is an essential component of a comprehensive HIV prevention strategy including efforts to develop a vaccine(s). Epidemiologic studies, including those related to vaccine preparedness research, provide opportunities for intervention research in defined cohorts of well-characterized populations. Strategies that employ therapies, devices, and other approaches (e.g., STD control, topical microbicides, and access to needle/syringe exchange programs) using HIV seroconversion endpoints are useful approaches for proving epidemiologic causation and evaluating effectiveness in preventing or reducing HIV transmission. As has been the case in AIDS clinical research, representatives of the HIV-affected community can make valuable contributions to the planning and implementation of intervention research studies.

Objective:

1.A **Develop new and expand current successful biomedical and behavioral integrated intervention strategies to reduce or prevent HIV transmission in both domestic and international settings.**

Strategies:

- Develop and maintain the infrastructures to identify populations in the United States and throughout the world with incidence and prevalence suitable for recruitment into vaccine and other intervention trials for preventing HIV transmission (e.g., trials of microbicides, barriers, STD treatment, multidrug therapy, behavioral interventions);
- Develop and evaluate methods to access, recruit, and retain known hard-to-reach populations for preventive intervention studies;

- Support development and evaluation of improved, acceptable, effective, and safe physical and chemical barrier methods including noncontraceptive methods to prevent sexual transmission of HIV and STDs;
- Develop strategies and conduct studies in a manner relevant to the developed and developing world to evaluate vaccines, drugs, and other interventions such as short-course antivirals, cesarean sections, vaginal cleansing, breast-feeding practices, nutritional interventions, and other approaches that may prevent perinatal transmission;
- Develop and assess the effectiveness of multiple approaches that may decrease HIV transmission among drug users, such as needle/syringe exchange, treatment of drug abuse, and decontamination of injection equipment;
- Develop and evaluate biomedical and integrated behavioral interventions to control STDs as a means of preventing HIV transmission;
- Evaluate potential risks and benefits of providing prophylaxis against infection following occupational and nonoccupational exposures to HIV;
- Evaluate the effects of contraception choices on STD/HIV transmission through sexual and perinatal routes;
- Evaluate the effects of access to, acceptability of, and compliance with prevention interventions on perinatal, sexual, and drug-use associated transmission of HIV;
- Examine the impact of population-level interventions on HIV transmission in communities, such as social normative behavior changes, economic opportunities for women, mass or syndromic approaches to STD control, and use of family planning programs to diagnose and treat STDs;
- Evaluate new, improved, and cost-effective methods to prevent transmission via blood transfusion in developing and developed countries; and
- Evaluate the potential long-term complications of vaccines, antiviral therapy, and other therapy used to reduce transmission on the development of chromosomal damage, mutagenesis, or carcinogenesis.

Scientific Issue:

Epidemiologic studies provide a critical knowledge and resource base for more basic investigations of HIV pathogenesis. A better understanding of human immunodeficiency virus characteristics and host factors that mediate disease progression; infectious, hormonal, pharmacologic, and behavioral factors that influence progression; and predictors of disease progression will be important in furthering attempts to develop anti-HIV vaccines and more effective therapeutic interventions against HIV and its sequelae.

Objective:

1.B **Elucidate through epidemiologically based studies the progression of HIV infection, from its earliest stages through long-term sequelae, and assess the effects of interventions on disease progression.**

Strategies:

- Elucidate the pathogenic mechanisms mediating HIV disease progression in well-defined subsets of individuals;
- Investigate the impact of intensive combination or new antiretroviral regimens during all phases of HIV infection on disease progression, quality of life, and survival;
- Investigate the role of potential cofactors and mediators of disease progression, including host genetic factors; infectious agents, including other retroviruses; hormonal factors such as pregnancy, contraceptives, and hormonal replacement; drug use; reexposure to HIV; and interventions such as nutritional supplementation, exercise, and health-enhancing behaviors;
- Develop approaches for identification of recently exposed and newly infected infants, adolescents, and adults for studies on the pathogenesis of early infection;
- Investigate the influence of HIV viral factors including genotype, phenotype, and drug resistance on disease progression;

- Study HIV-infected infants and children to determine (1) factors related to divergent rates of disease progression, (2) mechanisms that contribute to impaired growth and neurodevelopment, (3) impact of childhood infectious diseases and the safety and efficacy of immunizations for these diseases, (4) childhood-specific complications, and (5) the impact of treatment interventions on the above; and
- Assess the effectiveness and impact of immunizations and natural infections on disease progression in HIV-infected populations.

Scientific Issue:

Understanding the role of risk factors and mechanisms of HIV transmission is critical to the development of biologically and behaviorally based strategies to interrupt transmission of HIV. Epidemiologic studies provide important biological and behavioral information, including information on the role of other factors that may reduce or enhance transmissibility.

Objective:

1.C **Characterize the risk factors and mechanisms of HIV transmission in both domestic and international populations, with the goal of preventing transmission.**

Strategies:

- Evaluate the impact of improved therapies on HIV infectiousness and transmission;
- Evaluate HIV transmission and acquisition in relation to the following:
    - Viral factors such as viral concentration in blood, genital and oral secretions, and at mucosal sites; characteristics of HIV (genotype, phenotype, and drug resistance); and HIV infection stage;
    - Host intrinsic factors such as menstrual cycle, cervical ectopy, pregnancy, menopause, hormone replacement, circumcision, mucosal immunity, and immunologic and genetic determinants;
    - Environmental factors including intercurrent STDs, exogenous irritants, other causes of oral and anogenital inflammation, contraceptive use, hormonal replacement, drug abuse, and preexisting infection with other microbial agents;
    - Therapeutic factors such as immunomodulators, antibiotics for other infectious agents, and vaccines; and
    - Social and ecologic factors associated with infection including demographic factors such as socioeconomic status, race, ethnicity, age, and access to health care;

- Further define the timing, mechanisms, and risk factors in perinatal transmission, including breast-feeding;
- Determine the long-term effects of *in utero* exposure to HIV and antiretroviral prophylaxis to prevent perinatal transmission including the emergence of drug resistance in both HIV-infected mothers and infants;
- Evaluate the occurrence of transient HIV infection and the mechanisms by which it may occur; and
- Identify and characterize the factors related to resistance to HIV infection, including genetic, immunologic, and virologic factors, in persons who remain uninfected despite perinatal, sexual, or parenteral exposure.

Scientific Issue:

Most morbidity and mortality in HIV-infected persons result from the occurrence of OIs and malignancies. Strategies to prevent these illnesses include prevention of exposure to the etiologic agents, prevention of disease in those who are exposed, and prevention of disease recurrence. With the profound effects of combination antiviral therapies on viral levels and possible effects on immunocompetence, additional epidemiologic data are needed in order to design more effective strategies to prevent the occurrence of HIV-related OIs and malignancies and develop treatments for them.

Objective:

1.D **Undertake epidemiologic research to reduce or prevent the occurrence of infections, malignancies, and other serious health outcomes in HIV-infected persons.**

Strategies:

- Continue long-term followup of cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of disease in HIV-infected populations;
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections in HIV-infected populations; and
- In HIV-infected populations, evaluate risk factors and develop and assess interventions that reduce or prevent the following:
    - Infectious diseases;
    - Malignancies and associated oncogenic infections; and
    - Other HIV-associated diseases, including central and peripheral nervous system diseases and wasting syndrome.

Scientific Issue:

Epidemiologically defined populations provide insights into HIV transmission, including resistance and susceptibility to infection and infectiousness, and progression of HIV-related disease from early infection through long-term sequelae. The development of innovative biomedical, behavioral, and analytical methodologies that can be applied to epidemiologic studies will greatly increase understanding at the biological level and will help to identify strategies for prevention of transmission and disease progression.

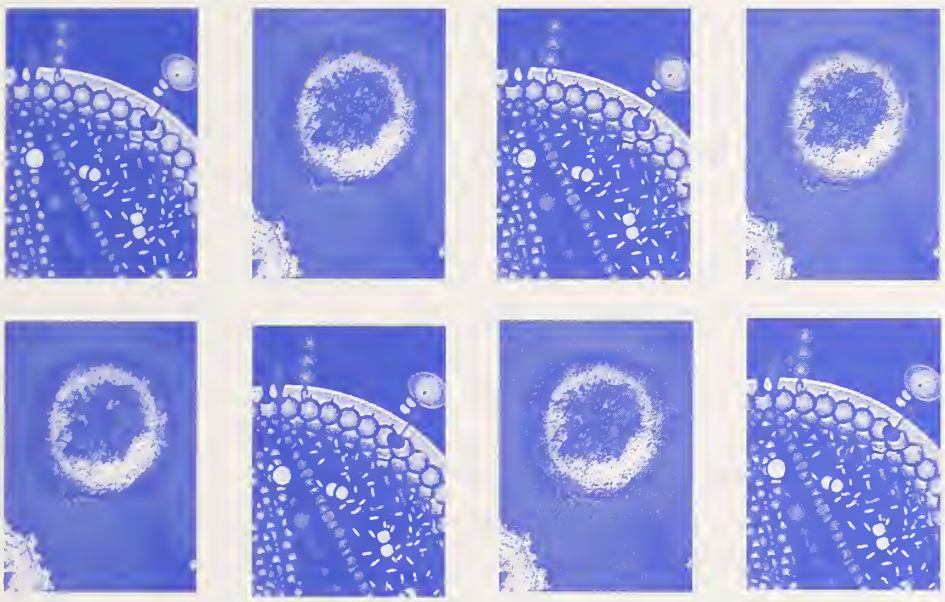
Objective:

1.E **Develop and evaluate new laboratory assays, information technologies, sampling methodologies, and statistical techniques for epidemiologic studies.**

Strategies:

- Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, and genetic assays suitable to large-scale epidemiologic research;
- Develop survey and sampling methodologies for hard-to-reach populations;
- Develop new biostatistical techniques to better characterize transmission dynamics, monitor and interpret disease trends, and study disease progression;
- Develop innovative approaches for record linkages that respect privacy issues to better study HIV-associated diseases and mortality;
- Develop, maintain, and effectively utilize national specimen repositories and databases for interdisciplinary HIV-related studies;
- Develop the application of modern information technologies to facilitate the conduct of HIV research in managed care settings;
- Develop rapid and inexpensive diagnostic assays for STDs;

- Develop and evaluate mechanisms for effective dissemination of HIV information to researchers, health care providers, and the general public that affects prevention and disease progression in developed and developing countries; and
- Support a comprehensive program of interdisciplinary methodologic research on statistical design and analysis of clinical trials with multiple interventions, community randomized HIV-prevention trials, and studies of the role of social networks in HIV transmission.



Etiology and Pathogenesis

AREA OF EMPHASIS:

Etiology and Pathogenesis

Status

In the quest for vaccines to prevent HIV infection and more effective drugs to contain the infection and treat the OIs, tumors, and other manifestations of a dysfunctional immune system, a better understanding is needed of how HIV infection is established and what causes the profound immune deficiency and terrible complications that accompany infection. What role do the specific products of HIV (the viral genes and their protein products) play in the viral life cycle of individual cells and within the body of infected individuals? How is HIV transmitted between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other systems that HIV afflicts? What host factors and cofactors influence the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies and OIs that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of etiology and pathogenesis research.

Since the initial isolation of HIV in 1983 and its identification as the causative agent of AIDS shortly thereafter, tremendous progress has been made in understanding the genetic structure and variability of the viral genome, critical aspects of the virus life cycle, and the functions of essential viral gene products. The knowledge that has emerged from basic research in these areas provided the foundation for all efforts to develop effective therapies to treat HIV infection. Progress in these areas, much of it fueled by support provided by NIH, continues at a rapid pace. Indeed, it is likely that more is now known about the fundamental biology of HIV than any other virus that causes disease in humans; yet much more still remains unknown.

While the fundamental principles of the HIV life cycle have been defined in an expeditious fashion, insights into how HIV establishes infection, replicates, persists, and causes disease in infected people have been more difficult to obtain. However, the concerted efforts by numerous NIH-sponsored investigators are now yielding impressive discoveries that are advancing our understanding of the disease process. The development and functioning of the human immune system have been the focus of significant interest and scrutiny and about which great discoveries have emerged. However, the fundamental complexity of the immune system operates in both health and disease. Better understanding of the normal functioning of the immune system will be necessary if we are to understand the pathogenesis of AIDS. Likewise, a better understanding of the pathogenesis of AIDS will yield important insights into the normal immune system and how it also may fail in conditions such as autoimmune disease or common infections and malignancies that are seen in persons not infected with HIV.

The challenge of understanding HIV infection and disease also represents an extraordinary example of how the biology of other infectious diseases may be studied in the future. Never before has the behavior of an infectious organism within an infected human been examined in such detail. For this type of investigation, new research tools are required to facilitate sensitive, high-resolution analyses. The amount of virus present in an infected person must be determined and its level of replication and consequent damage measured. The need to understand HIV infection has driven technological developments in this area, and much of this effort has been fueled by support provided by NIH.

The powerful tools recently developed to monitor the location and extent of HIV replication within infected persons have elucidated critically important details of how HIV infection leads to AIDS. Application of these new tools has revolutionized our understanding of the extent of HIV replication that takes place in infected people and how virus replication is directly linked to the destruction of T cells and the resultant compromise of the immune system. The broad outlines of the pathogenic mechanisms of HIV disease are now known, but the precise details of the process await definition. An improved understanding of these issues is necessary to permit definition of the optimal ways to use therapies to treat the primary HIV infection and its associated opportunistic complications.

The process of developing new drugs is based on the study of the fundamental structural properties of the relevant target of drug design. The basic research knowledge that represents the foundation of the concept of rational drug design emerged, in large part, from basic research supported by NIH and the pharmaceutical industry over a number of years. Although the potential benefits of this approach to drug development have yet to be fully realized, it will have applications to all aspects of human health and disease. It is likely that the effort to develop effective therapies to treat HIV infection and its associated conditions will provide a critical proving ground for the concept of rational drug design and a source of great experience for the refinement and advancement of its methods. Already, new and extremely potent antiviral drugs have been developed using basic research results concerning the HIV life cycle. The derivation of these drugs would not have been possible without the elucidation of the structure and function of two of the critical viral enzymes, reverse transcriptase and protease.

The challenge remains to develop even more effective treatments for HIV infection. The inherent ability of HIV to develop resistance to antiviral drugs must be overcome. This will require a continued effort to delineate the structure of HIV gene products and the molecular and structural basis for drug resistance. In addition, continued progress in understanding the intricate details of the virus life cycle, both within individual cells and within infected

people, will permit identification of new targets for antiviral drug development and determination of the most effective ways to use these drugs. As in the past, it is likely that continued progress in the development of new and more effective treatments for HIV infection will benefit from the productivity and creativity of NIH-supported investigators.

While significant progress has been made in understanding HIV disease and developing more effective treatments, a vaccine to prevent HIV infection remains an elusive goal. Because of the unique features of HIV infection, it is considered unlikely that an effective HIV vaccine will emerge from the same type of empirical developmental efforts that have produced many of the available, effective vaccines such as those to prevent polio virus or measles virus infection. A much better understanding of the mechanisms of transmission of HIV between individuals and the process by which the infection becomes established and persists is essential. Likewise, improved understanding of the nature of the immune response that contains, albeit temporarily, the replication of HIV and its resultant damage in infected persons, is necessary. NIH continues to be the major sponsor of basic research in these critical areas.

HIV Transmission

HIV-1 is transmitted through various routes: sexual, parenteral, and perinatal. Worldwide, sexual contact, primarily heterosexual intercourse, is the dominant mode of HIV-1 transmission, accounting for more than 80 percent of all incident infections. Examples of the responsive efforts supported by NIH in this area include the prior and current investigations of transmission in cohorts and collections of blood and sexual fluids for the genotypic and phenotypic characterization of viruses. The factors that determine the ability of an HIV-infected person to transmit the virus are not completely understood and therefore are also under active investigation by NIH-supported researchers. Studies are directed at understanding the contribution of cell-free versus cell-associated virus; the influence of high viral loads in blood, semen, urine, cervical/vaginal secretions, and oral fluids of the transmitter; and the effect of the transmitted viral strain phenotype on HIV transmission.

The variables that may influence a person's susceptibility to HIV-1 infection following exposure also have yet to be clearly defined. Recent findings on the resistance to HIV-1 infection of multiply exposed subjects bearing a homozygous deletion in CCR5, the gene encoding the recently described coreceptor for primary HIV-1 isolates, highlighted the importance of coreceptor utilization in HIV-1 transmission. These findings also suggest that the early interaction of HIV with target cells at the portal of entry is critical for the subsequent establishment of infection. NIH-funded research is therefore giving special emphasis to studies aimed at defining the role of components of the mucosal compartment, cellular and molecular aspects of mucosal immunity, viral and host genetic factors, and other

infectious agents and STDs on HIV-1 susceptibility and transmission.

Pathogenic Mechanisms of HIV Infection From Acute-Stage Infection Through Clinical Latency to Advanced Disease

Ongoing research at the molecular, cellular, and organ-system levels is elucidating the pathogenic mechanisms of HIV infection. Recent studies have shown that newly infected patients experience a high rate of viral replication and that, in an as-yet unpredictable manner, their immune systems undergo changes that continue until the development of AIDS. Research at the cellular and molecular levels includes studies of the mechanisms by which HIV enters and infects various cell types; the interaction between the viral regulatory elements and infected cells that appears to be directed at maintaining a persistent infection; the mechanisms of inappropriate immune activation; the net balance among various types of immune cells and the immunomodulatory growth factors expressed by those cell types; and the viral- and host-mediated mechanisms that influence the level of viral expression seen in successive stages of HIV disease.

NIH-supported investigators demonstrated that significant levels of virus are present in plasma during all stages of HIV infection, including the clinically asymptomatic phase, and that active virus replication is directly linked to the destruction of T-cell populations in infected individuals. This new understanding of the magnitude and kinetics of HIV replication *in vivo* has great implications for understanding and potentially overcoming the obstacle to effective antiviral therapy that is posed by the development of viral variants that are resistant to the inhibitory effects of antiviral drugs. The quantitation of HIV in plasma provides a new, direct virologic endpoint for monitoring virtually all infected people and may be of particular utility in assessing antiviral efficacy in clinical studies, especially in early-stage disease, where conventional virologic markers are often negative. In addition to measuring viral burden, NIH-sponsored investigators are characterizing the breadth and specificity of the anti-HIV immune response as a possible factor in a longer period of clinical latency.

To further understand the interaction between the virus and host immune system response, NIH is placing particular importance on the study of the *in vivo* effects of HIV infection. NIH-sponsored longitudinal cohort studies constitute a major resource for this type of pathogenesis research. Specific cohorts, such as long-term non-progressors, HIV-exposed but uninfected individuals, and rapid progressors, will provide clues for treatment and vaccine research by helping to characterize immune response profiles and provide information on correlates of immunity.

In vivo research into mechanisms of viral immunopathogenesis also utilizes animal models. All the available animal models contribute to our understanding of disease mechanisms. Continued support of *in vivo* research is a high priority at NIH.

There are hypotheses regarding AIDS pathogenesis in which either genetic or environmental factors or other infectious agents, in addition to HIV infection, may promote specific disease manifestations. For example, a novel herpesvirus has been identified in KS tissues and may prove to be the causative agent of this malignancy. Other such factors, often referred to as cofactors, may enhance or retard HIV transmission and/or alter the rate of progression from HIV infection to the development of symptomatic disease.

HIV Pathogenesis Affecting Women and Maternal-Fetal Transmission

In response to the changing demographics of HIV infection, studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. As part of this effort, NIH supports a number of epidemiologic cohort studies specifically focused on women, adolescents, and children. The study of patient samples and data generated by these cohorts is providing critical information about mechanisms of transmission and the course of disease progression in these populations.

Current basic research studies relevant to HIV-infected women focus on the characterization of cells susceptible to HIV infection in both the lower and upper reproductive tract and the influence of hormonal modulation on viral infectivity and vaginal immunity.

In the area of maternal-fetal transmission, studies have demonstrated that the transmission rate of HIV from mother to infant is between 20 and 35 percent. Transmission of HIV-1 from a mother to her infant may occur *in utero* through transplacental passage of virus, during delivery, or postnatally through breast-feeding. A recent large NIH clinical trial has determined that administration of zidovudine during gestation and labor and to the infant after birth significantly reduces the rate of HIV transmission. Ongoing clinical trials will help in defining the optimal timing for delivery of antiviral therapy to limit maternal-fetal transmission, the mechanism of the protective effect, and whether new antiviral agents and treatment modalities may be even more effective.

Many basic issues associated with maternal-fetal transmission remain unclear and are actively under investigation. These include the specific mechanism involved and the point in time at which HIV transmission occurs between mother and infant; whether specific strains (macrophage tropic or T-lymphocyte tropic) of the virus are more likely to be transmitted; the possible correlation between elevated maternal HIV-1 RNA levels in plasma or vaginal secretions and an increased risk of neonatal infection; the delineation of the role of maternal immunity in prevention of transmission to the fetus; and the role of cofactors such as substance abuse and concomitant infections in the efficiency of transmission.

Disease Manifestations

HIV infection affects the functioning of virtually all the organ systems within the body. Current NIH-supported basic and clinical studies are focused on the characterization of HIV/AIDS-associated diseases and on the assessment of their relative contribution to the overall disease progression in AIDS. The availability of new and more effective antiviral drugs and treatment modalities is having a beneficial effect on the course of HIV infection and might alter its manifestations. The influence of new antiretroviral therapies, able to lower viral load to undetectable levels, on the natural history of AIDS is also providing an unprecedented opportunity to gain insights into the pathogenic mechanisms underlying the disease manifestations associated with HIV infection and AIDS.

AIDS-Related Malignancies

AIDS is associated with a broad spectrum of neoplasms, including KS, lymphomas, cervical and anogenital carcinomas, Castleman's disease, leiomyomas, leiomyosarcomas, and hepatitis B-related hepatocellular carcinomas. The proportion of malignancies and their incidence rates might increase as the development of effective antiretroviral therapies and prophylaxis against OIs leads to prolonged survival of HIV-infected patients in the immunodeficient state. Immune deficiency is clearly linked with development of some types of lymphomas in HIV-1- and HIV-2-infected subjects and Simian immunodeficiency virus (SIV)-infected macaques. NIH-supported investigators are trying to clarify the mechanistic role of chronic stimulation mediated by viral and cellular proteins, high levels of growth-promoting cytokines present in HIV-infected subjects, and human DNA and RNA viruses and their direct or indirect interaction with HIV in the development of AIDS-associated malignancies. Studies of AIDS-related KS have highlighted the potential role of a newly discovered human herpesvirus, angiogenic growth factors, and HIV proteins released in the extracellular milieu in the etiology of this neoplasm. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate in the identification of new targets for disease prevention and treatment.

Neuropathogenesis

Neurological disease and neurobehavioral dysfunction associated with HIV infection cause considerable morbidity and mortality in afflicted children and adults. These manifestations include diseases associated with opportunistic infection of the brain resulting from the underlying immunodeficiency and the AIDS dementia complex, a disorder that is unique to HIV infection. NIH-supported research is directed at understanding how HIV infection contributes to nervous system damage through direct interaction of HIV with neuronal and nonneuronal cells and indirect mechanisms, such as those mediated by cytokines and neurotoxins released in response to the infection or the local inflammatory response to the infection. Important areas of ongoing research include

the determination of how HIV enters, establishes infection, and persists in the different compartments of the CNS, and the correlation between the extent of HIV replication *in vivo* and the incidence and severity of neurologic complications. The possible role of the CNS as a reservoir of HIV infection in the setting of antiviral therapies with limited CNS bioavailability is also under investigation. Special emphasis in all these studies is given to *in vivo* models of neuropathogenesis and to the integration of basic research studies on the neurologic complications of AIDS with natural history studies and ongoing clinical trials.

Opportunistic Infections

HIV infection results in progressive damage of the immune system of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-1-infected individuals. OIs can affect virtually every tissue and organ system in the body, resulting in severe functional compromise. OIs will clearly remain a major manifestation as long as immunodeficiency is the inevitable result of progressive HIV infection. NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated OIs. Currently supported research is directed toward developing methods to culture and grow these pathogens *in vitro*; developing animal models to study disease pathogenesis; identifying new targets for therapeutic interventions; and facilitating discovery and development of prophylactic and therapeutic agents. Special emphasis is given to the interactions between the pathogen and the host and its immune system. This will permit a better understanding of the establishment of infection, mechanisms of immune control by the host, evasion by the pathogen, and the contribution of the host immune response to disease.

NIH-funded researchers are studying viral infections by HSV-1 (herpes simplex virus-1) and -2, VZV (varicella-zoster virus), CMV, HHV-6, HHV-7, and JCV (JC Virus); fungal infections by candida, cryptococcus, and histoplasma; bacterial infection by *Mycobacterium avium* and *Mycobacterium tuberculosis*; and protozoal infection by cryptosporidium, microsporidium, *Pneumocystis carinii*, and *Toxoplasma gondii*. Since OIs remain the most important complication of HIV infection and the principal cause of death in HIV-infected individuals, understanding the fundamental biology and pathogenesis of these organisms will translate into new or more rational approaches to the prevention and treatment of their associated diseases.

Wasting

Wasting is one of the most devastating aspects and one of the major causes of morbidity and mortality in AIDS. Weight loss in AIDS results in a significant reduction in survival, independent of other factors influencing survival, including CD4 cell count and history of infection or malignancy. The etiology of wasting associated with AIDS is complex and multifactorial.

Critical loss of lean body mass is the hallmark of wasting in AIDS. AIDS patients with wasting illness escape a homeostatic control system and fail to generate normal responses to weight loss.

Alterations in energy expenditure, metabolic and endocrine abnormalities, and cytokine disregulation have all been implicated in the pathogenic mechanisms underlying the wasting syndrome. Wasting occurs episodically and is a manifestation of secondary diseases such as infections and gastrointestinal disease. OIs are associated with episodes of rapid weight loss, as cytokine-mediated inflammatory and immune responses occurring during these infections induce metabolic disturbances and have a profound effect on food intake inducing anorexia which may be a major contributor to weight loss.

Available interventions for the wasting syndrome in adults and related failure to thrive and growth retardation in children are either poorly effective or very expensive. Elucidation of the factors contributing to wasting will allow effective therapies to be tailored to the specific mechanism by which wasting occurs, with the potential for prolonging life and enhancing its quality in AIDS patients.

Organ-System-Specific Complications of HIV Infection

Organ-system-specific manifestations also attend HIV infection and disease. Gastrointestinal dysfunction and malabsorption are commonly observed in HIV-infected subjects. The gastrointestinal tract is one of the most important routes of transmission of HIV and the intestinal lymphoid tissue represents a major site of viral replication. CD4+ T-cell depletion has been shown to occur exclusively in the intestine in the early stages of infection in the SIV model. NIH-supported researchers are investigating the contribution of OIs, acquired deficiencies in intestinal enzymes, malignancies, and potential HIV infection of cells in the gastrointestinal tract to the gastrointestinal complications observed in HIV-infected individuals. HIV infection is also associated with multiple endocrine alterations probably reflecting critical interaction between the endocrine and the immune system. HIV-associated heart, renal, hematologic, pulmonary, and mucocutaneous complications also represent a cause of morbidity in infected subjects. The pathogenetic mechanisms involved in all these AIDS manifestations are not well understood and are under investigation. Their definition will permit a more rational approach to both preventative and therapeutic interventions.

Scientific Issue:

The mechanisms of HIV transmission and the early events in the establishment of infection need to be better understood.

Objective:

2.A **Delineate the viral, cellular, and molecular mechanisms involved in the transmission and establishment of HIV infection in adult and pediatric populations.**

(The scientific objectives 2.A and 2.B are of equal weight.)

Strategies:

- Delineate the relative efficiency of transmission of cell-free and cell-associated virus at different portals of entry;
- Delineate the molecular mechanisms by which virus-encoded genes, gene products, and cellular factors regulate HIV replication and influence transmission and establishment of HIV infection;
- Determine the role of viral phenotype/genotype and load on transmission of cell-free and cell-associated virus;
- Determine the structures of viral and host proteins responsible for key events in the transmission and establishment of HIV infections;
- Determine the cell or tissue type that serves as the portal of entry of HIV and the mechanisms by which STDs and other processes may influence HIV transmission;
- Identify host factors (including genetic and nonspecific) that mediate resistance or sensitivity to infection and delineate their mechanisms of action;
- Identify host factors (including immunologic, genetic, and nonspecific) that influence the ability of an HIV-infected person to transmit HIV infection to others;
- Define the cellular and immune mechanisms that inhibit/enhance the early events in the transmission and establishment of HIV infection;

- Study the biology of the mucosal immune system, including the cellular elements and regulatory processes responsible for the generation of immune responses;
- Identify biologic, environmental, social, and host factors determining relative efficiency of HIV transmission in various populations, especially developing versus developed world populations; and
- Elucidate unique aspects of the biology of HIV transmission in diverse and underresearched populations.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, and *ex vivo* models to examine the transmission and establishment of lentiviral infections; and
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, information databases, and quantitative virologic and immunologic assays.

Scientific Issue:

Basic scientific information regarding mechanisms that underlie HIV-related immune dysfunction and viral pathogenesis is critical to all areas of AIDS research.

Objective:

2.B **Delineate the viral, cellular, and molecular mechanisms associated with the pathogenesis of HIV-related immune dysfunction in adult and pediatric populations.**

(The scientific objectives 2.A and 2.B are of equal weight.)

Strategies:

- Determine the impact of early events in the establishment and systemic spread of HIV infection on the clinical course of the disease;
- Define the virologic (including load, phenotype, and genotype), host (including immunologic, genetic, and nonspecific), pharmacologic, and environmental factors that contribute to disease progression and nonprogression;
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo,* in the setting of both drug-naive and drug-treated individuals;
- Delineate the mechanisms of host immune control of HIV replication and how the effectiveness of immune control may vary depending upon the identity and location of infected host cells;
- Delineate the molecular mechanisms by which virus-encoded genes, gene products, and cellular factors regulate HIV replication and influence pathogenesis;
- Determine the structures of viral and host proteins involved in the processes that underlie disease progression;

- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune target cells/tissues, focusing on
    - Mechanisms by which HIV infection leads to the loss of individual CD4+ T lymphocytes;
    - Impact of HIV infection on T-cell population numbers, specificities, and functions;
    - Mechanisms of virally triggered immunopathogenesis, including immune activation, induction of nonresponsiveness, dysregulation in the number and function of immune (effector) cells other than T lymphocytes, and production of host factors, including cytokines and other soluble mediators;
    - Pathogenic mechanisms by which HIV infection leads to the structural and functional compromise of primary and secondary lymphoid organs, including hematopoietic precursor cells and their microenvironment;
    - Mechanisms by which HIV infection influences the developing immune system;
    - Mechanisms by which HIV infection disrupts host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations; and
    - Evaluation of whether and to what extent viral-induced damage can be reversed following suppression of HIV replication by therapeutic interventions;
- Determine the life span and developmental pathways of T lymphocytes; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age;
- Define markers and functional assays that will enhance our understanding of and ability to study immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system;
- Elucidate unique aspects of the biology of disease progression in diverse and underresearched populations;
- Define the reservoirs of virus infection that permit HIV persistence in the setting of effective antiretroviral therapies; and
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, and *ex vivo* models to examine the pathogenesis of lentiviral infections; and
- Promote programs to facilitate augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, information databases, and quantitative virologic and immunologic assays.

Scientific Issue:

Knowledge about the origins and pathogenesis of HIV-related cancers is urgently needed.

Objective:

2.C **Elucidate the etiologic factors, cofactors, and mechanisms in the pathogenesis of HIV-related malignancies. Enhance a bidirectional flow between basic and clinical observations and intervention programs on HIV-related complications, and foster interdisciplinary collaborations.**

(The scientific objectives 2.C through 2.F are of equal weight.)

Strategies:

- Elucidate the role of HIV infection and its associated immune dysfunction in the development of HIV-associated malignancies;
- Elucidate the role of infectious agents other than HIV in the development of HIV-associated malignancies;
- Identify the mechanisms by which immune dysregulation, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of HIV-associated malignancies; correlate these molecular factors with epidemiologic studies;
- Identify the characteristics of the host that predispose to development of malignant disease, including genetic, hormonal, and growth factors and immunologic characteristics;
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies and evaluate how the manifestations of HIV-associated malignancies are altered by such therapies;
- Identify novel pathogens that may contribute to the development of AIDS-related malignancies; develop new methodologies for novel pathogen identification; and

- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models and patient specimens for HIV-associated malignancies.

Scientific Issue:

It is critical to understand the neuropathogenesis of HIV-1 infection in both the central and peripheral nervous systems and the relationship of nervous system infection to disease progression.

Objective:

2.D **Elucidate the mechanisms underlying HIV-associated neurological disease and neurobehavioral dysfunction in adult and pediatric populations. Enhance the flow of information between basic, clinical, and behavioral research, and foster interdisciplinary collaborations.**

(The scientific objectives 2.C through 2.F are of equal weight.)

Strategies:

- Determine the cellular and molecular bases and pathogenic mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction, including
    - Identify how HIV enters, establishes infection, and persists in the CNS;
    - Identify the specific cells and regions of the brain involved;
    - Determine the relationship of virologic, immunologic, pharmacologic, and environmental factors to HIV-associated CNS dysfunction;
    - Determine the consequences of the biologic activity of cytokines and other soluble mediators on the CNS in the context of HIV-1 infection; and
    - Develop methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS in living subjects;
- Determine the impact of HIV/CNS infection on systemic disease progression and the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection;
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders;

- Investigate aspects of HIV infection that uniquely influence the developing nervous system;
- Delineate the role of OIs and drug treatment in neurologic and neurobehavioral complications of AIDS, including CNS dysfunction and peripheral neuropathies;
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies; and
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.

To facilitate the research goals listed above:

- Develop and employ appropriate animal models (e.g., nonhuman primate models) of CNS-lentivirus infection that best reflect specific aspects of the human HIV/CNS disease course or treatment that are crucial to understanding neurobehavioral and neurologic disorders;
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, cataloged, classified, stored, and distributed; and
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.

Scientific Issue:

It is critical to understand the processes of establishment of infection and development of disease for the HIV-associated OIs.

Objective:

2.E **Elucidate the pathogenic mechanisms of HIV-related OIs in adult and pediatric populations. Enhance a bidirectional flow between basic and clinical observations and intervention programs on HIV-related complications, and foster interdisciplinary collaborations.**

(The scientific objectives 2.C through 2.F are of equal weight.)

Strategies:

- Conduct studies of the basic biology and pathogenic mechanisms of opportunistic pathogens and their interactions with the host, including definition of
    - Portals of entry of opportunistic pathogens into the human host;
    - Processes that underlie the establishment and spread of infection; and
    - Mechanisms of tissue and organ system damage;
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease;
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs;
- Identify and elucidate the genetic and environmental risk factors associated with susceptibility to and development and progression of OIs;
- Study the effects of OIs on immune dysfunction and HIV disease progression;
- Elucidate the mechanisms of immune function that mediate protection against the OIs;
- Develop and validate assays of opportunistic pathogen-specific immune responses;

- Characterize the molecular and phylogenetic relationships of major AIDS OI pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs;
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated OIs and evaluate how the manifestations of HIV-associated OIs are altered by such therapies;
- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs in HIV-infected subjects; and
- Study clinical syndromes seen in HIV-infected persons that are not associated with known opportunistic pathogens in order to identify novel pathogens and characterize their biology and pathogenic mechanisms.

Scientific Issue:

It is critical to understand the etiologic and pathogenic mechanisms of HIV-related wasting and growth retardation.

Objective:

2.F **Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation. Enhance a bidirectional flow between basic and clinical observations and intervention programs on HIV-related complications, and foster interdisciplinary collaborations.**

(The scientific objectives 2.C through 2.F are of equal weight.)

Strategies:

- Define the etiologic and pathogenic mechanisms of HIV-related wasting (including studies performed on appropriate animal models) that may be operative at various stages of disease;
- Elucidate the virologic and immunologic consequences of HIV infection that result in wasting, impaired growth and development, malabsorption, and anorexia;
- Elucidate the pathogenic mechanisms by which OIs, hormonal dysregulation, and other consequences of HIV infection lead to wasting, impaired growth and development, malabsorption, and anorexia;
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated wasting, failure to thrive, and growth retardation; evaluate how the manifestations of HIV-associated wasting, failure to thrive, and retardation are altered by such therapies; and
- Determine factors associated with clinical response and lack of response to therapeutic interventions against AIDS-associated wasting syndrome and failure to thrive.

Scientific Issue:

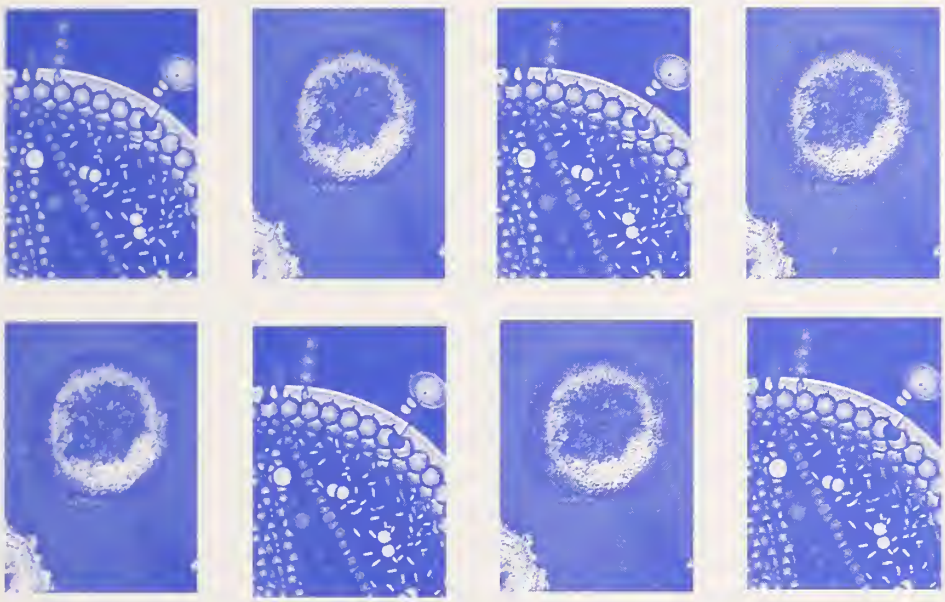
It is important to understand various other organ/tissue-specific complications of HIV infection.

Objective:

2.G **Elucidate the etiology and pathogenesis of HIV-related disorders in adult and pediatric populations: gastrointestinal, renal, endocrine, cardiovascular, cutaneous, hematologic, oral, pulmonary, and other diseases.**

Strategies:

- Investigate the etiologic and pathogenic mechanisms of HIV-associated gastrointestinal disease, including those responsible for varying manifestations of disease in diverse populations;
- Identify the etiologic and pathogenic mechanisms of HIV-associated nephropathy (HIVAN), including those responsible for varying manifestations of disease in diverse populations;
- Investigate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease;
- Investigate the etiology and pathogenesis of additional HIV-related disorders including autoimmune disorders and cardiovascular, cutaneous, hematologic, oral, pulmonary, and other organ/tissue-specific disorders as they compromise organ system development and function;
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies; and
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.



Therapeutics

AREA OF EMPHASIS:

Therapeutics

Status:

Two important scientific advances of 1996 have had a direct impact on HIV preclinical and clinical therapeutics research. The first was the demonstration that potent new combinations of antiretroviral drugs (usually including an HIV protease inhibitor) reduce viral load in many patients to below the limits of detection of current assays, some of which detect copy numbers of HIV-RNA less than 100 copies/mL. While antiretroviral-naive individuals (never having taken antiretroviral drugs) typically have the best responses, a substantial proportion of antiretroviral-experienced patients respond well to combinations containing at least two new drugs.

The short-term success of potent three-drug combinations demand additional research to maximize the likelihood of continued success. The most compelling questions include (1) How long can the virologic, CD4, and clinical responses be maintained on an initially successful regimen? (2) What are the earliest detectable signs of failure that indicate that changes should be made to the drug regimen? (3) What are the most common reasons for failure of these regimens? And (4) can treatment strategies aimed at minimizing the risk of clinical progression be developed? In terms of drug discovery research, the synergistic potency of combination regimens that combine one or more reverse transcriptase inhibitors with a protease inhibitor confirm that inhibition of more than one critical viral enzyme is a promising approach to treatment. Therefore, the development of new agents designed to inhibit one or more of the other known enzymatic or regulatory proteins of HIV has become an even higher priority.

If viral replication is not completely supressed by antiviral treatment, drug-resistant strains of HIV emerge, viral load increases, and disease progression may occur. Because currently available drugs are difficult to take, have significant toxicities, and have the potential for frequent drug interactions that may alter their potency and tolerance, the opportunity for incomplete suppression resulting in "viral escape" is significant. Systematic studies are needed to improve our understanding of the interplay of biomedical and behavioral factors affecting adherence; to optimize dosing in relation to the individual's metabolism, virologic response, and tolerance; and to develop new compounds and regimens that are easier to take and are active against viral strains resistant to existing drugs.

The second scientific advance of 1996 with a major impact on drug discovery and therapeutic research was the identification of several HIV coreceptors critical for viral entry into the cell. These discoveries have opened exciting research opportunities that focus on virus/host initial interactions, including a better understanding of receptor biology and the role of chemokine receptors in genetic susceptibility to HIV infection. Applied research is needed to design novel

therapeutic entities, preventive agents, and strategies to restore immune functions of HIV-infected individuals progressing to AIDS.

In addition, important incremental advances have been made in the area of medical management of OIs. Improved understanding of the use of therapeutic and prophylactic agents have advanced the options available to people living with AIDS. Challenges remain in combating infections for which no therapies are available, in stimulating drug discovery toward more effective and less toxic alternatives, and in improving the understanding of the pathogenesis of OIs within the setting of HIV-induced immune deficits.

The successes in therapeutics research of the past few years highlight the need for continued and improved collaborative efforts between Government- and industry-sponsored drug development and clinical trials evaluation efforts, so that the benefits patients are now seeing in improved quality of life and survival will continue until a normal life span for HIV-infected individuals becomes routine.

Therapeutic Discovery and Drug Development

The clinical testing of new therapies designed to reduce the adverse clinical outcomes of HIV infection, HIV-associated OIs, malignancies, and CNS dysfunctions requires active preclinical drug discovery and development programs. NIH supports several approaches in the area of therapeutic discovery, including screening of compounds for activity and rational drug design. The screening approach involves the testing of compounds that inhibit HIV replication and activity. Rational (targeted) drug development involves characterization and delineation of the structural biology of HIV and its components for the purpose of developing agents targeted at inhibiting specific steps in the HIV life cycle.

NIH-sponsored, investigator-initiated research contributes to and supports comprehensive drug discovery and development efforts. For example, basic biomedical research on HIV pathogenesis provides important information that serves as the foundation for successful drug discovery and development. NIAID complements these efforts with more specialized programs that augment, enhance, and accelerate the discovery and translational process. The National Cooperative Drug Discovery Groups for HIV (NCDDG-HIV) and the National Cooperative Drug Discovery Groups for the Treatment of the Opportunistic Infections Associated with AIDS (NCDDG-OIs) are designed specifically to expand collaborative efforts among academia, industry, and Government researchers interested in undertaking comprehensive therapeutic discovery and development efforts in these areas. The National Institute of General Medical Sciences (NIGMS) Targeted Antiviral Program provides extramural investigators with access to sophisticated techniques, while a similar program has been established for NIH intramural scientists through the IATAP.

Program projects and associated R01s organized to support structure-based targeted drug design have resulted in structure determination of several HIV components, including integrase, RNaseH, p24, reverse transcriptase, and the Zn fingers of the nucleocapsid. Potential inhibitors of these compounds are currently being tested. The NIAID-supported Strategic Program for Innovative Research on AIDS Treatment Strategies (SPIRAT) is designed to accelerate the translation of novel therapeutic strategies from bench to bedside via iterative laboratory and clinical research, and clinical proof-of-concept demonstrations in small, pilot clinical studies.

Together, these and other investigator-initiated programs have resulted in the discovery and/or development of several FDA-approved antivirals with activity against HIV reverse transcriptase and protease enzymes. They include the nucleoside analog reverse transcriptase inhibitors zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and lamivudine (3TC); the protease inhibitors saquinavir, indinavir, ritonavir, and nelfinavir; and two nonnucleoside reverse transcriptase inhibitors, nevirapine and delavirdine.

In addition, several new viral and host/cellular targets have been identified, and aggressive efforts are under way to develop agents to block or compete with their function. Examples include the recently identified host cell chemokine coreceptors necessary for HIV infection, CCR5 and CXCR4; a zinc-binding domain in the HIV nucleocapsid protein involved in viral packaging; a nuclear localization signal in the HIV matrix protein, which is critical for transport of proviral DNA into the host genome; HIV accessory proteins, including Nef, Vpu, Vpr, and Vif, all of which are involved in HIV infectivity, replication, and/or pathogenesis; other host factors required for HIV replication, such as cellular kinases, cytoskeleton components, nuclear components, which may provide novel agents for therapeutic development that are less likely to mutate to drug-resistant forms; and better tolerated and more active protease inhibitors, which penetrate into HIV sanctuary sites in the body.

Scientists also are exploring novel molecular and genetic strategies to slow or halt HIV replication. Such strategies include developing molecular approaches to present HIV antigens to the immune system with the objective of stimulating immune reactivity against HIV; endowing cytotoxic T cells with the ability to recognize and destroy HIV-infected target cells; improving DNA-based therapeutic vaccines to augment and/or enhance cell-mediated and humoral (antibody-based) immune responses in infected patients; and developing gene-based therapies that modify natural target cells (e.g., CD4) with anti-HIV genes to prevent virus replication.

Drug Development and Evaluation—Primary Disease

The development of therapeutic regimens to block HIV infection or delay disease progression while maintaining quality of life is the major goal of the therapeutic research effort. During the past several years, remarkable progress has been made in our understanding of the pathogenesis of HIV infection, information that has been instrumental to the recent rapid progress in drug discovery and development. At the same time, we have a new class of potent antiretroviral drugs and sensitive new assays for measuring the level of HIV in the body, greatly improving the therapeutic armamentarium of the physician treating infected individuals.

The most significant development in this regard during 1996 was the approval by the FDA of three agents in a potent new class of antiretroviral drugs, the protease inhibitors. This class of agents targets a different viral enzyme from that inhibited by the earlier antiretroviral agents, and the two-pronged approach results in synergistic antiviral activity when drugs from both classes are combined. For the first time in the epidemic, a large proportion of patients treated with these new (usually triple) combinations of agents (referred to as "highly active antiretroviral therapy," or HAART) experience a profound fall in their plasma viral load, often to undetectable levels as measured by currently available quantitative assays. In more advanced patients with HIV-related symptoms and/or OIs, the profound reduction in viral load may be accompanied by a rise in CD4 cell count and in many cases amelioration of these symptoms.

Not only has the development of HAART provided researchers with new opportunities to study the pathogenesis of HIV disease, but the demonstration of high levels of viral replication throughout the long period of clinical latency has resulted in a new focus for therapeutics research on patients with acute infection (within several months of initial infection). The research hypothesis under study in these patients at the current time is whether aggressive HAART can prevent replication and spread of HIV within the body so profoundly that, over several years, the infection is eradicated.

Although this goal of viral eradication, or cure, may not be attainable, given the high levels of viral replication within weeks of infection and rapid dissemination throughout the body, there is still the hope that early potent treatment may be able to permanently reduce the "set point," or steady state, of viral replication that emerges within 6 to 12 months of initial infection in newly infected but untreated individuals.

For the vast majority of persons infected with HIV who are beyond the acute phase, life-long antiretroviral treatment with potent combinations remains the best hope. As long as the drugs suppress viral replication, resistance to them should not develop, although HIV that continues to replicate in "sanctuary sites," where drug concentrations are lower than in the blood, may represent an opportunity for resistant strains

to emerge. The immediate challenge, then, is to develop new drugs and treatment approaches that are potent, penetrate into all parts of the body, promote adherence, and are well tolerated over the long run, with minimal risk of failure.

Even with the availability of safe and effective antiretroviral therapy, it is likely that immune-based therapies, particularly those with the capacity to restore lost immune function, will still be needed, especially for those individuals at more advanced stages of immune depletion. Interleukin 2 (IL-2), which has been studied intensively by intramural scientists at NIAID, is the best example at this time of an immune-based therapy that has the potential to add clinical benefit. Discussions are underway regarding the design and implementation of a large controlled study to determine whether the typical rise in CD4 counts following treatment in many individuals translates into real clinical benefit.

Future research in therapeutics will focus on the development of easier-to-use protease inhibitors, more potent and better tolerated reverse transcriptase inhibitors, and the development of drugs targeted against other enzymes critical for viral replictation, such as integrase. In addition, the recent identification of cofactors necessary for the entry of HIV into cells will spawn an intense effort to identify and develop pharmaceutical agents with the ability to block entry of HIV into susceptible cells at the cell surface, which is the earliest event in the viral replication cycle.

Drug Development and Evaluation of Anti-OI Agents

Discovery and development efforts in AIDS-related OIs have resulted in four new drugs approved by the FDA in 1996 for clinical use: azithromycin for prevention of bacterial infections in patients with advanced HIV disease; cidofovir for treatment of CMV retinitis; ganciclovir implant for treatment of CMV retinitis; and a liposomal formulation of daunorubicin for treatment of HIV-related KS.

NIH, through its intramural and extramural programs, has developed a multifaceted approach to the discovery, development, and preclinical and clinical evaluation of anti-OI agents. Priority is placed on the identification of effective strategies where established therapies do not exist and on the evaluation of new agents with the potential for improving efficacy or reducing toxic effects of existing treatment or prophylactic regimens. OIs represent the most common cause of morbidity and mortality of HIV-infected individuals.

Biomedical research on OIs is particularly challenging because of the limited understanding of the basic biology and natural history of the causative microorganisms; the lack of *in vitro* culture systems for susceptibility testing and biochemical studies; the lack of targeted screens or rational design of new agents; the need for better animal models for testing treatment and prophylactic regimens; the need for evaluation of drug combinations for efficacy and safety, drug interactions, pharmacology, and

immunotoxicology; and the relatively low level of interest shown by pharmaceutical manufacturers in the development of agents against HIV-associated OIs.

Preclinical and clinical therapeutics research is targeted on the most prevalent and medically challenging opportunistic pathogens. These include CMV, *Mycobacterium avium* complex (MAC), infectious causes of diarrhea (cryptosporidium, microsporida), *Mycobacterium tuberculosis,* pathogenic fungi (including candida and cryptococcus), *Pneumocystis carinii*, *Toxoplasma gondii,* and other opportunistic pathogens (JCV and herpesviruses), bacteria, and endemic mycoses.

Scientific areas of emphasis include strategies for prevention and suppression of infection, understanding of the pathogenesis of each disease and interaction with HIV infection, development of improved methods to quantify the infectious load and to monitor response to therapy, and development of strategies to control drug resistance.

Development of Agents for AIDS-Related Malignancies

NCI, NIAID, and their sponsored investigators have collaborated since 1992 in the development of an AIDS Malignancy Program, which consists of the following components:

- The AIDS Malignancy Bank (AMB), funded by NCI since the fall of 1994, consists of 5 main member institutions and approximately 30 affiliated institutions. The AMB provides access to the research community at large of well-characterized tumor tissue, biological fluids, and demographic and clinical data from HIV-infected patients with malignancies. Proposals to utilize the AMB are reviewed three times per year.

- The AIDS Malignancy Consortium (AMC), funded by NCI since the fall of 1995, consists of 13 clinical trials members and one data management, operations, and statistical center. The AMC conducts early-phase clinical trials that utilize the expertise of both NCI and NIAID-sponsored scientists. In addition to assessing potential antitumor activity and drug–drug interactions, these clinical trials also evaluate the impact of therapy on viral load and underlying immune function.

- The NCI Clinical Trials Cooperative Groups, funded by NCI for many years, are a well-established clinical trials network engaged in the evaluation of new cancer treatments. They have received set-aside funding since 1994 to pursue clinical trials in men, women, and children with AIDS-related malignancies, which include non-Hodgkin's lymphoma, primary CNS lymphoma, KS, and HPV-related malignancies, such as cervical cancer. Investigators from both the AMC and Cooperative Groups are working together in developing complementary research agendas and are donating

specimens to the AMB and using it as a repository.

- The AIDS Malignancies Working Group (AMWG) consists of extramural scientists and internal NIH scientists and staff who represent a spectrum of disciplines working with AIDS malignancies. NCI convened the first meeting of the AMWG in February 1996, and their charge is to identify research opportunities and to provide recommendations on research priorities and resource needs.

In addition, NCI has consolidated their intramural clinical efforts in the recently created HIV and AIDS Malignancy Branch.

Clinical Trials

NIH has the primary responsibility for the federally supported clinical trials efforts in the evaluation of potential therapies for the treatment of HIV infection and its sequelae. NIH supports a diverse network of clinical trials programs, which includes the Adult AIDS Clinical Trials Group (AACTG), the PACTG, the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA), Studies of the Ocular Complications of AIDS (SOCA), and the AMC. More than 50,000 patients have been enrolled to date in NIH-sponsored clinical studies, which have involved the evaluation of nearly 80 agents.

Past accomplishments of NIH-sponsored clinical trials include demonstration of the efficacy and clinical benefits of ZDV (zidovudine) for both adults and children with early and asymptomatic infection; the safety and efficacy of ddI and ddC for HIV-infected adults and children; the benefits of ddI and ddC in patients who are intolerant of or who have failed ZDV treatment; the antiviral activity of interferon and its benefits for reducing KS lesions; the utility of paclitaxel in advanced KS; the benefits of nimodipine for the treatment of AIDS dementia complex; and the therapeutic benefits of ddC plus ZDV combination therapy.

In 1994, the results of a landmark NIH-sponsored clinical trial were reported, which demonstrated that ZDV administered during gestation and labor and to the infant after birth reduces the rate of HIV transmission from infected mother to infant by approximately two-thirds.

Accomplishments of NIH-sponsored clinical trials over the past 2 years include the completion of two combination nucleoside trials in the adult and one in the pediatric HIV-infected populations that demonstrated the clinical superiority of ddI monotherapy and ddI/ZDV combination therapy over ZDV monotherapy; another pediatric trial demonstrating that combination ZDV/3TC and ZDV/ddI are superior to montherapy with either ZDV or ddI in terms of disease progression or death; and other NIH-sponsored trials that have shown clinical benefit of thalidomide in the treatment of oral aphthous ulcers, recombinant human growth hormone for treatment of AIDS-associated Wasting Syndrome (AWS), and megestrol acetate for AWS.

Additional NIH trials have contributed to the understanding of the use of protease inhibitors, such as saquinavir, indinavir, ritonavir, and nelfinavir; nucleoside analog reverse transcriptase inhibitors, such as d4T and 3TC; and nonnucleoside reverse transcriptase inhibitors, such as nevirapine and delavirdine, including the impact of these agents on viral load and on clinical outcomes. For further understanding of HIV pathogenesis, small clinical studies have been conducted using potent new combinations of agents to explore the viral cycle, viral turnover, and CD4 turnover and to investigate the development of mutations predictive of resistance.

Accomplishments in combating HIV-associated OIs include demonstration of the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX), atovaquone, dapsone, and aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia (PCP) in patients intolerant of TMP-SMX; TMP-SMX for prophylaxis of recurrent PCP; aerosolized pentamidine for prophylaxis and treatment of PCP; fluconazole for the treatment of cryptococcal meningitis and prevention of fungal infections; foscarnet for the treatment of CMV retinitis; IV gamma globulin for reducing OIs in HIV-infected children; the combination of pyrimethamine and clindamycin for toxoplasmic encephalitis; and itraconazole for disseminated histoplasmosis.

Antiretroviral and OI prophylaxis regimens are becoming more complex with respect to drug–drug interactions and adherence.

Pediatrics

Transmission of HIV from mother to child is the predominant source of HIV acquisition and is unique to pediatric HIV infection. In 1994, the NIH-sponsored clinical trial ACTG 076 demonstrated that ZDV administered during gestation and labor and to the infant after birth reduces the rate of perinatal HIV transmission by nearly 70 percent. There are encouraging data now available in studies from multiple geographic areas in the United States as well as in Europe that indicate when the ACTG 076 ZDV regimen is incorporated into routine clinical practice outside of a clinical trials setting, overall perinatal transmission rates show similar declines.

Data from ACTG 076 indicate that lowering of maternal viral load (as measured by HIV-RNA levels) accounted for only a portion of the observed efficacy of the ZDV ACTG 076 regimen. These data imply that an important component of protection may be pre- and postexposure prophylaxis of the infant. Further evaluation of reasons why some infants become infected in spite of ZDV treatment is ongoing.

An important priority is the development of simpler and less expensive interventions for interruption of vertical transmission, which will facilitate treatment in the United States and the developing world, where proportionately the larger share of HIV infection in women and children occurs.

It is estimated that approximately 14,000 infected children were alive in the United

States as of 1996. Even with 100 percent implementation and full efficacy of the ACTG 076 ZDV regimen, more than 500 newly infected infants are expected to be born annually. New antiretroviral and OI therapies will need evaluation in these infected children, particularly regarding the pharmacokinetics, toxicity, and response profiles which vary by age owing to organ immaturity and ongoing development.

In pediatrics, growth failure and neuro-developmental problems are the most common manifestations of HIV disease, and progression typically occurs more rapidly in infected children than adults. New data indicate, in contrast to what is observed following primary infection in adults, that high HIV-RNA plasma levels persist in perinatally infected children, declining very slowly over the first 2 years of life.

The virologic response of children to combination therapy may be less than that observed in adults, indicating that earlier use of more potent combinations in infants may be required.

Because administration of therapeutic agents occurs during periods of organ system development in the growing child, an important component of therapeutic research in pediatrics is the long-term followup of children for possible late-occurring adverse outcomes.

Specific preclinical and clinical projects in pediatric HIV infection will include:

- The development of improved animal models for perinatal HIV transmission to better understand mechanisms and timing of transmission and for evaluation of the efficacy of interventions to reduce transmission;

- The evaluation of the potential for transplacental carcinogenicity of different antiretroviral agents in appropriate animal model systems;

- Studies to improve our understanding of why some infants become infected with HIV despite the administration of ZDV and to evaluate other interventions to prevent perinatal transmission (such as use of potent combination antiretroviral regimens);

- The evaluation of short-term and long-term effects of exposure to antiretroviral agents *in utero* in uninfected as well as infected infants born to women who have received antiretroviral agents during pregnancy;

- Studies to better define the kinetics of HIV replication and CD4+ cell generation following perinatal infection;

- Evaluation of the safety, risks, benefits, and antiviral effects of immediate initiation of antiretroviral therapy during primary infection in infants (perinatal period);

- Evaluation of the pharmacokinetics, safety, and antiviral efficacy of potent antiretroviral drug combinations in

infected pregnant women, HIV-exposed neonates, and infected infants, children, and adolescents;

- Development of improved therapeutic regimens for managing HIV infection and its associated conditions in children and evaluation of the potential late toxicities of antiretroviral agents; and

- Development of immunomodulatory therapies for treatment and immune reconstitution in infected children (including passive/active immunization and gene therapy).

Participation of Underrepresented Populations

It is important that the participation of specific populations in NIH-funded clinical trials reflect the changing demographics of HIV infection and AIDS, including women, children, adolescents, drug abusers, IDUs, minorities, the urban poor, and individuals residing in rural areas. Recruitment and enrollment of these underrepresented populations is a high priority in NIH-sponsored studies and should be a consideration within each objective of this section. Whenever possible, interagency collaboration is fostered to enhance participation of these populations, including provision of ancillary services.

NIH has published and implemented new and strengthened guidelines for the inclusion of women and minorities in clinical trials.

The NIH-supported clinical trials programs strive to ensure that a sufficient proportion of minority participants are enrolled into the clinical trials so that the results of the research may be generalizable to the affected HIV population at large. NIH works with these networks to identify the need for and/or assist in the development of culturally sensitive education materials, identify real or potential barriers to recruitment and retention in clinical research for these groups, and identify mechanisms to overcome these barriers.

Pediatric clinical trials enroll principally minority populations. The NIAID/NICHD-funded collaborative PACTG enables the flexibility to adjust the location of trials sites to accommodate the changing epidemiology of HIV in women and children along with the establishment of advanced technology sites for investigators of pathogenesis in the context of clinical trials.

In addition, the ACTG supports the AIDS Clinical Trials Infrastructures in Minority Institutions to enhance HIV clinical research performed at minority institutions. Four institutions, located at Howard University (Washington, D.C.), Meharry Medical College (Nashville, Tennessee), the University of Puerto Rico (San Juan), and the University of Hawaii (Honolulu), received 4-year awards as adult ACTUs. This program increases the number of minority staff involved in ACTG research and the number of minority participants in the studies.

Drug-abusing populations are at risk for receiving intermittent or interrupted therapy. This should be considered in the development of therapeutics in terms of (1) developing delivery systems that minimize adherence demands, (2) understanding the implications of such interrupted treatment for each therapeutic regimen that is developed, (3) developing strategies for minimizing the undesirable effects of interrupted treatment, and (4) studying interactions between drugs of abuse and new anti-HIV and/or anti-OI pharmacotherapies in terms of alterations in pharmacokinetics, development of adverse consequences, or progression of disease.

Scientific Issue:

Because of the complex nature of HIV infection—e.g., the rapid rate of mutation and development of drug resistance—it is important to identify and develop novel therapeutics to inhibit viral and host factors required for HIV replication, particularly therapies that impact at different stages of the life cycle of the virus.

Objective:

3.A **Improve understanding of the structure and function of potential viral and host molecular targets; design and develop predictive *in vitro* and *in vivo* test systems. Conduct discovery and preclinical development of novel agents and therapeutic strategies (e.g., immune-based, gene-based) directed against viral and/or host factors involved in HIV replication, including drug-resistant strains.**

Strategies:

- Identify and characterize new and/or understudied viral and host targets for anti-HIV therapy; develop predictive test models that simulate the *in vivo* situation to aid in the identification of agents and strategies active against these targets;
- Acquire structural information on HIV constituents and host cell components with which they interact (transcription factors, cytoskeletal elements, cyclophilins, kinases, etc.); make resolved structures available to publicly accessible databases in a timely manner; integrate structural information data with drug design efforts on known molecules and on new viral and host-specific targets (examples include p7-Zn finger, integrase, HIV accessory proteins [Nef, Vpu, Vif, Vpr], coreceptors CD4 and gp120, and host components required for replication); and use structural data for HIV proteins and host components as a basis for combinatorial design in the synthesis of small molecules with binding and inhibiting capacity;
- Identify host-encoded factors that confer protection from HIV infection and/or delay disease progression; identify cell factors involved in determining degree of HIV virulence in different susceptible cell lineages (e.g., monocyte/macrophages; T lymphocytes); define the cell-specific factors leading to viral integration,

transcription, assembly, and budding; and integrate this information with that from structurally driven efforts to design molecules with high activity and low or no adverse effects on cell viability and function;

- Conduct preclinical studies—when they cannot appropriately be done by industry—of new compounds and combinations of compounds and novel natural products, including assessment of toxicity, immunologic effects, pharmacokinetics, teratogenicity, transplacental carcinogenicity, fertility in animal models, and development of analytical methods and chemical formulations;
- Emphasize basic and applied research to advance development of gene therapy approaches to HIV infection and its complications; support viral and nonviral vector development to optimize gene delivery; develop new strategies for streamlining or eliminating the need for *ex vivo* manipulation of cells;
- Use animal and *ex vivo* models to study the biological and pharmacological characteristics of therapeutic compounds and strategies, transplacental and postpartum transmission of lentivirus, drug-specific parameters (dosages, time of initiation, duration of treatment, etc.), reduction or elimination of lentivirus from body reservoirs, and the impact of gene therapy on cell survival, immunological parameters, viral load, and clinical parameters;
- In animal models, evaluate transplacental passage of antiretroviral agents and the effects of these compounds on placental function and on fetal development and viability;
- Support the development and evaluation of new compounds to inhibit sexual transmission of HIV, including systemic agents, topical microbicides, HIV-specific virocides, and biologic approaches;
- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations leading toward resistance and cross-resistance; and study the structural basis of resistance for established targets;
- Evaluate the intracellular pharmacokinetics and activity of antiretroviral agents in various cell types and in various stages of the cell cycle; correlate intracellular pharmacokinetic parameters with drug toxicity/efficacy;
- Develop agents with desirable pharmaceutical characteristics, such as improved bioavailability, CNS penetration, and penetration of other known viral sanctuaries; and
- Develop formulations for both existing and experimental agents suitable for infants, children, and others who need them.

Scientific Issue:

Sustained HIV replication is a major factor in the pathogenesis of HIV/AIDS, and antiretroviral agents constitute an integral component of treatment of the disease. Clinical studies are necessary to determine agents and strategies that will prolong a disease-free state and survival in HIV-infected individuals.

Objective:

3.B **Conduct clinical trials and develop new trial methodologies to evaluate the safety and efficacy of new therapeutic strategies as rapidly as possible; optimize clinical efficacy and proper use of available modalities both in treatment-naive and in heavily pretreated HIV-positive individuals; define factors that affect the success of therapeutic strategies (including the role of adherence and resistance); and advance our understanding of disease pathogenesis and progression.**

Strategies:

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults and children to determine pharmacokinetics and tissue bioavailability, antiviral activity, effects on the immune system, toxicity, and clinical efficacy;
- Evaluate combinations of antiretroviral agents that are synergistic, toxicity-sparing, and non-cross-resistant in individuals with a variety of prior antiretroviral drug experience, including heavily pretreated individuals with advanced disease;
- Develop and evaluate virologic, immunologic, and clinical markers to assess drug activity; determine the prognostic value of surrogate markers in response to therapeutic interventions;
- Explore the determinants of drug failure of antiretroviral agents, e.g., malabsorption, suboptimal drug blood levels, drug resistance, and suboptimal adherence;
- Explore the utility of real-time antiretroviral phenotypic and genotypic assays in clinical trials enrolling a broad spectrum of patients;

- Evaluate the impact of transmission of drug-resistant HIV strains on disease progression and therapy;
- Support research on the effectiveness of pharmacologic approaches to improving adherence to antiretroviral regimens;
- Investigate drug interactions among commonly used treatments for HIV-related disease, its complications, and other substances that may be used by HIV-infected individuals—e.g., drug-abuse-treatment medications, oral contraceptives, other prescription drugs, nonprescription drugs, alternative or complementary therapies, and substances of abuse, including alcohol;
- Design and implement clinical trials to evaluate the effects of antiretroviral treatment of primary infection in adults and neonates, including assessment on subsequent clinical disease course and on virologic and immunologic markers;
- Determine the immunologic and virologic dynamics during primary perinatal infection; use this information, as appropriate, to develop surrogate outcomes in pediatric trials;
- Evaluate safety and toxicity of antiviral agents in pregnant women, including transplacental passage of the agents and safety to the fetus; evaluate the pharmacokinetics of drug elimination in the newborn;
- Evaluate the role of antiretroviral therapy or other treatment modalities administered in the immediate post-HIV-exposure period in preventing the establishment of HIV infection;
- When appropriate, evaluate potential gender-, race-, ethnicity-, and age-specific differences in drug efficacy and safety, including pharmacokinetics;
- Support clinical trials to evaluate the safety and efficacy of gene therapy;
- Evaluate potential delayed or late toxic effects of antiretroviral therapy (including hepatotoxicity and carcinogenicity) following short-term administration of prophylaxis regimens as well as with chronic treatment;
- Evaluate the impact of potent antiretroviral therapy on the reactivation of hepatitis viruses, the potential need for treatment of viral hepatitis in coinfected patients, and the development of late-stage complications of viral hepatitis;
- Develop a coordinated plan to evaluate the long-term efficacy of therapeutic strategies and to facilitate cross-protocol analyses and meta-analyses;
- Design methods to improve retention in clinical trials;

- Support research and development of more relevant clinical trial design and statistical methodology to evaluate more quickly and meaningfully the activity, clinical efficacy, and reasons for failure of new agents, and strategies for the treatment of HIV disease; and
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of antiretroviral agents.

Scientific Issue:

Progressive deterioration of immune function is an underlying cause of morbidity and premature mortality in HIV disease. The integrity of the immune system is an important component of improving clinical outcomes for HIV-infected individuals.

Objective:

3.C **Develop and evaluate therapeutic approaches that will enhance, restore, and/or maintain the immune systems of HIV-infected individuals and extend our understanding of immunopathogenesis.**

Strategies:

- Study the mechanisms of action of immunomodulating agents as therapeutics; proceed with preclinical studies of the most promising agents;
- Evaluate immunoactive strategies in clinical trials, taking advantage of opportunities to test specific hypotheses of HIV immunopathogenesis;
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials in adults and children;
- Accelerate the preclinical and clinical testing, including virologic effects, of cytokines, modulators of cytokines, and other immunoactive agents singly and in combination with antiretroviral agents, to prevent further immune deterioration and to reconstitute deficient immune systems in HIV-infected individuals; develop and evaluate active and passive immunotherapeutic approaches for the treatment of HIV infection and its sequelae;
- Support research on the effectiveness of pharmacologic approaches to improving adherence to therapeutic regimens;
- Evaluate the safety and efficacy of administering cellular elements in an autologous, syngeneic, allogeneic, or xenogeneic fashion, including use of expanded peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation;

- Develop new therapeutic strategies based on gene therapy approaches to protect hematopoietic stem cells and stromal elements from destruction by HIV;
- Evaluate the potential of inhibiting HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels and by developing agents capable of blocking HIV binding to coreceptors;
- Support the development of a cord blood bank from infants born to HIV-infected mothers in anticipation of future gene therapy trials;
- Explore the feasibility and utility of storage of lymphocytes and/or stem cells of HIV-infected individuals; and
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of immunoactive agents.

Scientific Issue:

OIs continue to be the most common immediate causes of morbidity and mortality in HIV-infected individuals; better therapeutic approaches to their prevention and treatment are important to improving clinical outcome.

Objective:

3.D **Discover and delineate the structure and function of potential molecular targets and agents for prevention and treatment of HIV-associated OIs, while improving understanding of the biology and pathogenesis of HIV-associated opportunistic microorganisms. Develop and evaluate new agents and strategies for preventing and treating OIs which decrease morbidity and increase survival.**

Strategies:

- Support discovery and preclinical programs to identify targets and to develop therapies, especially for cryptosporidium, MAC, microsporidia, JCV, CMV, HPV, and azole-resistant fungi, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics;
- Develop *in vitro* culture systems for OIs such as PCP, cryptosporidiosis, and microsporidiosis;
- Support and encourage mechanism-based screening of natural products and novel synthetic compounds to identify candidate agents for treatment of OIs; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing;
- Determine the high-resolution molecular structures for proteins from OI organisms; apply these structures to the design of inhibitors; make coordinates for resolved structures available in publicly accessible databases in a timely manner; and determine structures of other OI macromolecules (e.g., surface carbohydrates) as potential targets;
- Conduct preclinical studies—when they cannot appropriately be done by industry—of new compounds, combinations of compounds, and novel natural products,

including assessment of toxicity, immunologic effects, pharmacokinetics, teratogenicity, transplacental carcinogenicity, fertility in animal models, and development of analytical methods and chemical formulations;

- Develop animal models that predict efficacy of potential agents for preventing and/or treating OIs;
- Conduct clinical trials to evaluate agents for the prophylaxis and treatment of HIV-associated OIs; target OIs that have proven to be significant epidemiologically, including *Mycobacterium tuberculosis* infection, MAC, CMV-infection end-organ disease, HPV-associated disease, cryptosporidiosis, microsporidiosis, cryptococcosis, azole-resistant fungal infection, toxoplasmosis, PCP, acyclovir-resistant herpes infections, progressive multifocal leukoencephalopathy (PML), bacterial infections, and other infections made more deleterious by HIV;
- Support clinical trials that assess the impact of new antiretroviral regimens on the risks and manifestations of opportunistic conditions associated with HIV/AIDS in adults and children;
- Determine better strategies for simultaneous prevention of multiple OIs in the context of antiretroviral treatment; determine optimal time to initiate prophylaxis for different OIs; and develop improved OI strategies to minimize toxicities and the development of resistant organisms;
- Study the pharmacologic interactions of anti-OI therapies with antiretrovirals;
- Support clinical research in the context of drug abuse treatment to reduce OIs among HIV-infected drug abusers; develop and evaluate interventions to improve entry into treatment, retention, and adherence to therapy among multiple-diagnosed populations (e.g., substance abuse, mental illness, and HIV/AIDS);
- Study the bidirectional interaction of HIV infection and OI pathogens on pathogenesis, presentation, and disease outcomes in adults and children in the context of clinical trials of antiretroviral agents and OI drugs;
- Study the impact of primary acquisition of OI pathogens versus reactivation of latent infection;
- Evaluate immune-based therapies as adjuncts for treating OIs;
- Support research and development of new, more relevant clinical trial design and statistical methodologies to evaluate the activity, clinical efficacy, and reasons for failure of new agents and approaches in the treatment and prophylaxis of opportunistic complications of HIV disease;

- Develop clinically useful assays and methodologies for the rapid diagnosis of OIs, quantitative monitoring of therapeutic responses, and drug sensitivity testing of opportunistic microorganisms, especially *M. tuberculosis, M. avium*, enteric pathogens, *P. carinii*, CMV, fungi, toxoplasma, and JCV;
- Determine the role of preexisting immunity in controlling OIs;
- Develop OI-specific vaccines; determine the ability of HIV-infected individuals to respond to these specific vaccines throughout the course of HIV infection;
- Evaluate the safety, toxicity, and immunogenicity of previously unevaluated vaccinations against common infections in HIV-infected adults and children, including the short- and long-term effects on HIV replication;
- Support clinical trials to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs in HIV-infected infants, children, and pregnant women;
- Develop formulations of existing and experimental anti-OI drugs appropriate for use in infants, children, and other populations that need them;
- Develop, incorporate, and validate appropriate quality-of-life parameters into clinical trials of agents to prevent or treat OIs; and
- Support research on the effectiveness of pharmacologic approaches to improving adherence with anti-OI regimens.

Scientific Issue:

Vertical transmission of HIV from the infected mother to child is the predominant mode of transmission for pediatric HIV infection worldwide.

Objective:

3.E **Develop, evaluate, and implement strategies for interrupting vertical transmission of HIV from mother to child and extend our understanding of the pathogenesis of perinatal transmission and of early infection.**

(The scientific objectives 3.E through 3.G are of equal weight.)

Strategies:

- Define the mechanisms and timing of perinatal HIV transmission to facilitate development of targeted drugs/strategies to decrease perinatal transmission;
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring without compromising the treatment of the pregnant women; possibly include such strategies as antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, vitamin supplementation (e.g., vitamin A), HIV vaccines, adjuvants, and virucides, alone or in combination;
- Evaluate the safety, toxicity, pharmacokinetics, and antiretroviral activity of anti-HIV agents in pregnant women, fetuses, and newborns;
- Determine the transplacental transfer of anti-HIV drugs from mother to infant;
- Evaluate the risk of vertical transmission of drug-resistant HIV strains;
- Evaluate the influence on drug-resistant virus in the mother on the efficacy of regimens to prevent perinatal transmission;
- Study the effect of antiretroviral regimens used for maternal health indications on the risk of vertical transmission and other outcomes in offspring;

- Investigate interactions between drugs of abuse and anti-HIV therapeutics in pregnancy; evaluate the impact of such interactions on vertical transmission and disease progression;
- Support the long-term followup of women and children (including children ultimately found to be uninfected) who participate in perinatal trials to evaluate potential late effects of antiretroviral agents and/or biologics;
- Evaluate the potential mechanism for possible carcinogenic effects following *in utero* antiretroviral exposure;
- Support collaborative analysis of existing databases to evaluate potential obstetric interventions against vertical transmission, such as cesarean deliveries and other aspects of intrapartum care;
- Support research and development of new, more relevant clinical trial designs and statistical methodologies to evaluate the activity, clinical efficacy, and reasons for failure of new agents and approaches in the treatment of pregnant women and their offspring;
- Improve the sensitivity and specificity of diagnostic procedures that are accessible and cost-effective to permit the earliest possible determination of HIV infection in infants born to HIV-infected mothers; develop criteria to define early identification of infant infection in perinatal trials conducted in breast-feeding and non-breast-feeding populations; and determine if antiretroviral and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis;
- Support international collaborative efforts for the conduct of perinatal trials; and
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials for HIV-infected pregnant women.

Scientific Issue:

HIV-associated malignancies have a significant impact on morbidity and mortality, and some are expected to become increasingly common as survival with severe immune dysfunction is prolonged and as the demographics of HIV infection change. Recent advances in pathogenesis (e.g., KSHV/HHV-8) offer new potential areas for therapeutic intervention.

Objective:

3.F **Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of HIV-associated malignancies.**

(The scientific objectives 3.E through 3.G are of equal weight.)

Strategies:

- Identify novel mechanisms and targets (e.g., cytokines, angiogenesis, or hormonal) for treatment and prevention of HIV-associated tumors such as KS, non-Hodgkin's lymphoma, HPV malignancies, including anogenital dysplasias and cancers; develop new therapeutic strategies on the basis of these findings;
- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies (e.g., pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles);
- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KHSV/ HHV-8 and Epstein-Barr Virus [EBV], HPV, and hepatitis B) in their pathogenesis;
- Use structural biologic and biochemical information to rationally design therapeutic agents for the treatment of HIV-associated malignancies by targeting pathogenic mechanisms;
- Develop preclinical and *in vivo* models (e.g., severe combined immunodeficiency-human [SCID-hu] mice) for the testing of potential therapeutic strategies against HIV-associated malignancies;

- Develop *in vitro* models of KS and assays for angiogenesis inhibitors;
- Improve methods for early diagnosis of malignancies and for early detection of recurrent cancer;
- Design and conduct clinical trials to evaluate novel approaches to the treatment of AIDS malignancies and to evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection;
- Develop, incorporate, and validate clinical trial methodologies that include a measure of tumor-specific clinical benefit that correlates improvement in function with conventional objective measures of tumor response and a staging system that will have improved prognostic value for response and survival;
- Encourage collaborative studies within existing clinical trials networks to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce the risk or prevent the development of malignancies;
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors;
- Encourage clinical studies of HIV-infected patients with non-AIDS defining malignancies with emphasis on evaluating diagnostic and management challenges and the impact of therapy on virologic, immunologic, tumor parameters, and drug–drug interactions;
- Explore strategies for attenuating or preventing toxicities associated with therapy and effects of such strategies on virologic and immunologic parameters; and
- Support research on the effectiveness of pharmacologic approaches to improving adherence to complex therapeutic regimens in individuals with HIV-associated malignancies.

Scientific Issue:

HIV infection of the nervous system is a component of the biology of HIV that may require special therapeutic targeting. Both central and peripheral nervous system disorders are common and important causes of morbidity.

Objective:

3.G **Develop strategies for assessing, preventing, and treating HIV nervous system infection and the central and peripheral nervous system disorders complicating HIV infection.**

(The scientific objectives 3.E through 3.G are of equal weight.)

Strategies:

- Develop and evaluate novel strategies and agents that are active against putative pathways of HIV-induced CNS dysfunction in adults and children;
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury in order to identify agents that ameliorate HIV neuropathogenesis;
- Assess the pathogenetic role of viral sequestration in the CNS including its role as a reservoir of viral persistence and as a site of independent selection of antiviral resistant strains and other mutants;
- Design and conduct clinical trials addressing nervous system complications of HIV infection in adults and in children;
- Develop objective quantitative assessment (e.g., surrogate markers in cerebrospinal fluid [CSF], functional neuro imaging) that correlate with treatment efficacy;
- Develop therapeutic agents and/or delivery systems that are capable of crossing the blood–brain barrier; assess the safety and efficacy of these preparations; and develop agents that have the potential to block HIV entry into the CNS;
- Develop better strategies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected persons while improving knowledge of pathogenesis;

- Characterize the CNS pharmacokinetics and pharmacodynamics of antiviral drugs; determine the importance of CNS drug penetration in reducing CNS infection in neurologically symptomatic and asymptomatic subjects;
- Validate and enhance the efficiency of neuropsychological and neurologic tests performed in the context of clinical trials to identify those tests most capable of determining treatment-related changes in different age and cultural groups;
- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies;
- Monitor CSF for HIV viral load and immune activation markers in patients enrolled in studies of HAART;
- Support research and development of new, more relevant clinical trial design and statistical methodologies to evaluate the activity and clinical efficacy of new agents and approaches in the treatment of neurologic complications of HIV disease;
- Support research on the effectiveness of pharmacologic approaches to improving adherence to therapeutic regimens in neurologically impaired individuals with HIV infection;
- Develop, incorporate, and validate neurological functional and quality-of-life scales in clinical trials aimed at measuring neurologic outcomes; and
- Selectively incorporate neurologic and neuropsychological assessments into other HIV-related clinical trials.

Scientific Issue:

HIV affects many organ systems causing significant morbidity for which therapeutic management strategies are limited.

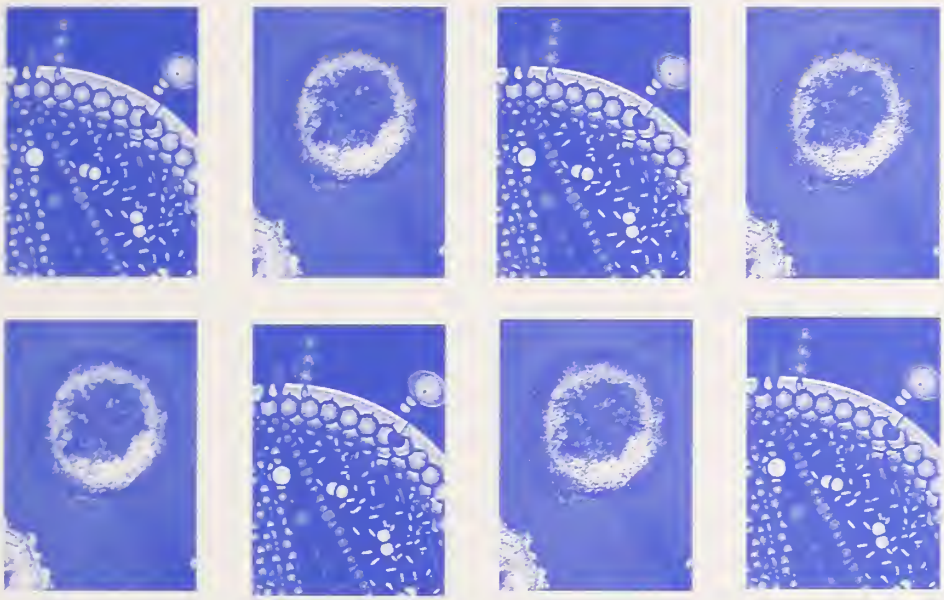
Objective:

3.H **Develop and evaluate better therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome and growth failure and hematologic, dermatologic, renal, metabolic, pulmonary, cardiac, gastrointestinal, endocrinologic, psychiatric, and oral manifestations.**

Strategies:

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection while increasing knowledge of their pathogenesis;
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of certain micro- and macronutrients (such as vitamins and trace elements), to delay the development of wasting and other complications of HIV disease, particularly in HIV-infected individuals who may otherwise be at risk of malnourishment;
- Support research and development of new, more relevant clinical trial designs and statistical methodologies to evaluate the safety, efficacy, and ultimate acceptability of new agents and approaches in the treatment of wasting syndrome, growth failure, and other complications of HIV infection;
- Support research on the effectiveness of pharmacologic approaches to improving adherence to therapeutic regimens;
- Develop, incorporate, and validate appropriate quality-of-life parameters into clinical trials of wasting and other complications of HIV infection; and
- Evaluate the safety and efficacy of alternative and complementary therapies in the management of complications of HIV disease.

and capacity building



Vaccines

AREA OF EMPHASIS:

Vaccines

Status:

Overview

Developing a vaccine or vaccines that are safe and effective in preventing HIV infection in exposed individuals is a major public health priority in the national and international effort to combat this pandemic. HIV disease continues to have a major impact on public health worldwide, and its spread is projected to increase through the year 2000 and beyond. The United Nations Joint Programme on AIDS (UNAIDS) has estimated that about 8,500 people become infected with HIV daily, of which 90 percent are in the developing world. If current trends persist, the rate of new infections will remain relatively stable in Europe and North America but will expand and devastate parts of Latin America, Africa, and Asia.

In the United States alone, more than 600,000 persons have developed AIDS, and as many as 850,000 are believed to be infected with HIV-1. The demographics of newly reported AIDS cases has been shifting to an increasing proportion in women, adolescents, and minorities. Even with the reduced number of AIDS deaths in the past year, it is estimated that there are 40,000 to 60,000 new infections occurring annually in the United States. New data indicate that trends for reduced risk of infections in homosexual populations may have reversed, particularly in young men, with the unsubstantiated belief that new drug combinations would provide a cure.

Finding effective means to control the human, social, and economic costs of HIV/AIDS represents one of the highest public health priorities. Behavioral interventions remain a critical component in preventing the spread of HIV, and delivery of effective drug therapy will decrease the number of AIDS deaths in the near term in the United States. These activities alone will not be sufficient to contain the epidemic, and vaccines may be the only cost-effective way to prevent HIV infection worldwide. Therefore, an affordable, safe, and effective vaccine that is also easily delivered and acceptable to various populations at risk is urgently needed.

To address the obstacles and facilitate HIV vaccine development, NIH has stepped up support for a broad program encompassing basic, preclinical, and clinical vaccine research on candidate vaccine products. To this end, the AVRC, headed by Dr. David Baltimore, has been established to increase the focus on new strategies for discovery and development of a safe and effective HIV vaccine. The AVRC identified three specific areas of basic research that were needed to support more effective vaccine research. These areas were understanding the structure and function of HIV envelope (env) protein; improving animal models to understand correlates of immune protection; and understanding the mechanisms of directing antigen processing *in vivo*. A new program of 2-year "innovation" grants were awarded in FY 1997 through NIAID to

encourage active support of these specific research areas. In addition, a cross-institute NIH Vaccine Laboratory effort has been initiated by focused staff discussions, and joint vaccine research will be funded through NIAID and NCI intramural programs beginning in FY 1998.

In parallel, NIH supports research on risk factors and other preventive interventions that will form an essential foundation for vaccine trials, in collaboration with other Federal agencies, local communities, industry, and international organizations.

Goals for a Preventive Vaccine

The goal of preventive vaccines is to slow and eventually end the HIV pandemic and to protect the individual from HIV infection and/or disease. Protective efficacy against HIV infection can be measured by a range of clinical and virological endpoints. Desirable goals of vaccination are to induce immune responses that quickly clear or reduce incoming virus and infected cells and, if HIV is established, to control viral replication and maintain a low viral load, thereby preventing disease progression and transmission. It may be unrealistic to expect an HIV vaccine to completely prevent HIV infection. Optimally, the vaccine-induced immune response would be capable of clearing virus and virus-infected cells. Thus, limited replication might occur at the site of entry, but disseminated infection would be prevented.

Control of viral replication, even if the virus is disseminated, could maintain a low viral load and/or reduce viral shedding, thereby preventing secondary spread of the virus to others. Vaccine-induced diminution in viral load also might be correlated with prevention or delay in disease progression; a correlation between low virus load and long-term nonprogression has been observed in both epidemiologic investigations and animal studies of pathogenesis and vaccines. Efficacy of vaccines in preventing established infection can be determined relatively early in the conduct of a vaccine trial by viral culture or PCR. However, assessment of long-term control of viral replication, or immunosuppression and disease progression, which may be critical for assessing efficacy, will make the conduct of efficacy trials more complex. This will be particularly true in populations with access to the highly effective multiple-drug therapeutic regimens early in the course of infection.

Vaccine efficacy may also be influenced by the dose of infecting virus and by the site or route of exposure. For example, a vaccine may protect against a low dose of virus at a mucosal site of sexual exposure but not protect against a large inoculum acquired intravenously. Alternatively, a vaccine may protect against exposure to virus intravenously but not protect against spread of HIV infection from an established mucosal site. Vaccine strategies therefore may need to be tailored for route of HIV exposure and may require combination approaches to optimize protection.

Various strategies for stimulating a protective immune response against HIV infection are being explored through basic

research, animal models, and clinical trials. There are many inherent uncertainties, not only in the identification of the immune responses required for protection against HIV infection or disease but also in the vaccine designs and strategies needed to induce such protective responses. Thus, multiple conceptual and practical approaches to development of candidate vaccines are being pursued at the preclinical level, with prioritization into small Phase I trials and additional selection and prioritization of candidates for further clinical study. Conducting small clinical trials affords the opportunity to return to the laboratory and refine those candidates that prove less than optimally immunogenic and permits rapid incorporation of vaccine improvements. Vaccines also may serve as immunomodulators to improve immune function and diminish HIV disease progression particularly in recently infected individuals and may potentially prevent transmission from mother to fetus or from one infected adult to another.

Basic Research Relevant to Vaccine Development

Basic research on HIV and the immune system provides crucial information required for the development of vaccine candidates. These efforts, however, are complicated by many unique aspects of HIV infection, including an unprecedented degree of antigenic variation. There are at least two major groups of HIV-1 (M and O), with each exhibiting several major genotypic subtypes (clades). Virus from one clade (B) predominates in the United States. However, there is extensive variation within a single clade and even in a single individual. This variation has been shown to affect recognition by and escape from both humoral and cellular immune responses. Vaccines capable of eliciting an immune response to a broad spectrum of antigenic specificities or to highly conserved epitopes will thus be required to protect against HIV infection.

Recent information suggests that antibodies (humoral immunity) from some infected individuals are able to effect broad neutralization of HIV subtypes. This suggests common epitopes, possibly related to the receptors and coreceptors of the virus that are expressed on widely divergent subtypes of HIV. In addition, recent data from both HIV-infected and HIV vaccine volunteers indicate that cytotoxic T cells also are able to recognize epitopes from widely divergent HIV.

The NIAID-sponsored HIV variation project is investigating the rate and magnitude of both genetic and antigenic variation in HIV and related retroviruses. The findings from this project will help determine the impact of such variation on strategies for developing potential AIDS vaccines.

The nature of the immune response needed to protect against HIV infection or to ameliorate established infection is poorly understood because much still needs to be learned about immune responses, in general, and those relevant to protection from viruses with the potential to establish

latency in infected cells, in particular. In this context, a great deal of new information will be necessary if one is to create vaccines that will be effective against a virus such as HIV that replicates within cells, specifically targets and destroys cells of the immune system, and can spread by cell-to-cell transmission. This includes knowledge concerning (1) the factors that regulate the induction of cytotoxic T cells that destroy virus-infected cells of various types, (2) the factors that determine whether effector immune responses that occur to key antigens are amplified rather than tolerized or deleted responses, (3) the factors that establish immunologic memory responses to antigens of interest so that protection is persistent, (4) the identity, source, regulation, and mechanism of action of cytokines or chemokines that affect, directly or indirectly, viral replication and persistence, (5) the signaling events that result in productive T-cell activation or interfere with responsiveness, (6) the role of antibodies in reducing virus load and/or controlling the spread of infection, (7) the mechanisms by which antibodies function to neutralize HIV and related viruses, (8) the role of antibody-dependent killing of infected cells, and (9) the interaction of humoral and cellular immune responses at mucosal sites to effectively contain viral infection.

Vaccine Strategies

Currently, NIH researchers are pursuing a multipronged approach for the development of HIV vaccines including traditional approaches such as the incorporation of killed viruses in known adjuvants and the development of attenuated viruses. There are serious concerns about the safety of these approaches that remain unresolved, but studies in animal models on killed and attenuated virus vaccines may help to reveal the correlates of immune protection and the requirements for an effective vaccine. However, the unique problems posed by HIV suggest a need for increased efforts to design novel approaches. Several being pursued include the use of synthetic viral peptides, recombinant proteins, and virus-like particles (VLPs). In addition, live recombinant vectors, vaccines composed of copies of the virus genome incorporated into the genomes of highly immunogenic but non-disease-producing carrier viruses such as vaccinia and avipox, are being studied. Other vaccines under evaluation in animal studies (e.g., adenovirus or poliovirus vectors) exhibit efficient delivery of antigens to selected compartments of the immune system, such as the mucosal area, where specialized immune responses particularly relevant to preventing entry of HIV are needed.

One area of emphasis is the design of more complex synthetic vaccine candidates capable of inducing both cellular and humoral immunity. This involves identifying segments of the HIV glycoprotein envelope and internal proteins, such as gag and RT, that induce immune-targeted helper T cells and cytotoxic T lymphocytes (CTLs). Another approach is the development of genetically engineered, noninfectious HIV mutants that lack the viral RNA genome or are crippled in such a way that the virus is unable to infect yet contains a full complement of

HIV antigenic proteins, which can assemble, potentially in more authentic structures such as VLPs, against which a protective response can be generated. VLPs can be produced in genetically engineered cell lines to decrease safety concerns.

One promising new approach to eliciting cell-mediated and humoral immune responses utilizes the direct injection of "naked" DNA encoding HIV antigens into muscle or other accessible tissues. Animals injected with DNA construct for the HIV *env* gene produced CTLs and humoral responses specific for the HIV envelope and produced antibodies that neutralized certain infectious HIV isolates *in vitro*.

These studies of potential vaccine candidates need to be expanded to include a far wider group of molecular, bacterial, and viral vectors and to include strategies that address the problems of intracellular HIV and viral latency. Nearly all of the first-generation vaccines that have reached evaluation in human volunteers were based on laboratory-adapted isolates of HIV that are more easily neutralized than macrophage-tropic primary HIV strains that are isolated early after infection in many individuals. Second-generation vaccines based on primary HIV isolates are just entering early research testing. Finally, combination approaches, sometimes referred to as "prime plus boost" strategies, need to be explored more fully to enhance the responses induced by only a single type of vaccine approach.

HIV/Chimpanzee Model

Some strains of HIV-1 can infect chimpanzees, thereby establishing an animal model to evaluate vaccines and infection with HIV-1. However, infections with most HIV isolates have not been accompanied by development of disease. After incubation periods exceeding 7 years, several chimpanzees have shown signs of immune suppression and AIDS. HIV-1 from the affected animals may have become adapted to chimpanzee cells and developed a higher pathogenic potential.

In vaccine studies utilizing the HIV/chimpanzee model, native or recombinant HIV *env* proteins and virus vectors carrying HIV protein genes have induced both cellular and humoral immunity. In addition, studies of *env* product vaccine candidates as well as more complex HIV vaccine strategies with recombinant adenovirus vectors or HIV DNA have shown efficacy in preventing HIV infection in chimpanzees. Hyperimmune anti-HIV immunoglobulin (HIVIG) and several monoclonal antibodies to envelope protein also have been evaluated for safety and potential to prevent HIV infection in chimpanzees under experimental conditions. Chimpanzees with persistent but apparently "attenuated" HIV infection have been exposed to other HIV isolates from the same or different clades in an attempt to learn whether immune responses that were not capable of clearing the initial infection were, nonetheless, capable of combating a new strain. Thus,

infected chimpanzees may provide a valuable resource for studying cross-reactive immune responses. NIH supports chimpanzee colonies and programs that evaluate vaccine candidates and products for passive immunity in this animal model. The importance of using more pathogenic-virus challenge stocks and routes of exposure that more closely approximate naturally occurring HIV strains has been appreciated, and new stocks are in development or being tested for strains found both in the United States and elsewhere.

Macaque Models

Key developments for various vaccine approaches have resulted from studies using SIV. The importance of this model rests with both the genetic relatedness of SIV to HIV and the AIDS-like syndromes that develop in several species of SIV-infected macaques. The higher viral load and disease endpoints, which have not been demonstrable in the chimpanzee model, are very important for vaccine development. Different SIV isolates provide virus/host interactions that exhibit different degrees of virulence reflecting the spectrum of HIV infections that occur in humans. More importantly, in addition to sterilizing immunity to prevent infection, macaque models permit investigation of vaccine effects that may be more realistic goals for initial human vaccines—protection against disease and vaccine modulation of viral replication. Experimental vaccines analogous to those being developed for clinical trials as well as other novel approaches are being evaluated in this model.

To date, vaccine approaches based on live attenuated SIV have exhibited the greatest degree of efficacy and provide opportunities for defining correlates of immune protection. Concerns for safety, particularly in infants, must be resolved before progress can be made with an attenuated HIV-vaccine approach. However, studies of attenuated AIDS vaccines in animal models may provide genetic constructs with improved safety for development of live-vector vaccines or VLPs, i.e., genetically "killed" vaccine approaches.

Chimeric viruses (SHIV) made by replacing the *env* gene (and other selected genes) of SIV with any of a variety of HIV-1 *env* genes show increased promise for vaccine evaluation in macaques. SHIV viruses infect and persist in macaques, and recent animal-adapted constructs have induced CD4 cell depletion, AIDS, and death. Vaccines containing HIV *env* components that are intended for human use can now be tested for immunogenicity and efficacy in macaques in a disease model. SHIV constructs that infect efficiently via the mucosal route and incorporate genes for env protein from non-clade-B HIV are being developed to evaluate vaccine-induced protection against divergent HIV isolates.

The pig-tailed macaque, *Macaca nemestrina*, which is susceptible to infection with selected stocks of HIV-1 and HIV-2, and baboons, which can be infected with some isolates of HIV-2, continue to be studied.

HIV-2 stocks have been developed that induce AIDS-like disease in *M. nemestrina* and baboons.

Other Animal Models

Human immune system tissues have been successfully transplanted into mice with SCID to create a system for testing vaccine candidates or components of the human immune response to HIV vaccines. While a wide range of viral isolates can be tested, incomplete repopulation with human lymphoid stromal cells and low numbers of repopulating human lymphoid cells have presented major limitations to use of this system.

Feline immunodeficiency virus (FIV) isolates that are pathogenic for cats now exist, and a vaginal transmission model recently has been developed. Its convenience and relatively low cost might make it an attractive model for analysis of biomedical agents to block transmission, such as microbicides. Vaccine experiments with cross-strain protection have been performed in this model and its relevance as an animal disease make this an attractive model for further vaccine studies.

Equine infectious anemia virus (EIAV) may provide a unique model to investigate the relevance of vaccine-induced enhancement of lentivirus disease as well as escape from protective humoral immunity.

Vaccine Development

NIAID has established HIV Vaccine Working Groups, which include representatives drawn from intramural scientists at NIH, NIH-sponsored extramural scientists, and community constituency groups, to assist in the scientific coordination and planning of NIAID efforts in targeted areas of vaccine design and correlates of immunity. The National Cooperative Vaccine Development Groups (NCVDGs) for the discovery and development of vaccine candidates will be competitively renewed as Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) grants in FY 1998 and FY 1999. The scope of the work may be extended in these awards to include early human clinical testing. Research teams comprising scientists from industry, academia, and Government collaborate to develop and test novel experimental HIV vaccine concepts in laboratory and animal models.

Several adjuvants such as immune-stimulating complexes (ISCOMs), muramyl tripeptide, Quil A or QS 21, liposomes, and MF59 have been studied in macaques for their ability to stimulate humoral and cellular responses as well as to provide protection against virus challenge with candidate vaccines. These as well as other adjuvants have now been studied in human clinical trials with HIV *env* vaccines with limited success. Novel approaches to

induce effective antigen presentation for both humoral and cellular immunity, as well as durable functional immune responses, are still urgently needed. Use of cytokines (delivered either as proteins, as DNA, or in vectors) to modify and focus the type of immune responses is an extremely active area of research in both mice and macaques.

Collaborative Mucosal Immunity Groups (CMIGs) initiated studies focused on induction and assessment of regional mucosal immune responses to HIV in human subjects as well as nonhuman primate models. Studies in this area are now open to competitive renewal and remain critical for prevention of infection in the worldwide pandemic.

Cooperation with Industry

Industrial partners will play an essential role in development of HIV vaccines and other biomedical interventions to prevent infection. Factors that affect the participation and collaboration of industrial partners need to be addressed. These include not only economic, legal, and regulatory issues but also scientific ones. Vaccines need to prevent HIV infection not only in the United States but worldwide. Collaborations must be established to provide relevant clinical isolates and information for the preparation and testing of such vaccines. Moreover, to facilitate the development of safe and efficacious vaccines, mechanisms should be adopted to promote further utilization of information generated from relevant animal models. Currently, few vaccine developers are pursuing the SIV/macaque models partly because of the need to develop unique reagents and methodologies and the extensive resources required. Collaborative programs between industrial, governmental, and academic agencies are needed to evaluate the comparative efficacy of parallel vaccine approaches against HIV and related retroviral models.

Vaccines and Immune Intervention Against Perinatal HIV Transmission

The ACTG 076 trial has demonstrated that transmission of HIV from mother to infant can be significantly reduced by use of a ZDV regimen given to HIV-infected pregnant women and their newborn infants. However, the complex ACTG 076 regimen is not practical for most of the developing world, where the largest proportion of HIV infection among women and children exists. An ideal regimen would be given once or only for a limited period of time, easily administered, nontoxic to mother and child, and inexpensive and have potential to prevent postpartum transmission via colostrum or breast milk.

The mechanism of the ZDV effect is not known, but initial studies indicate that ZDV therapy was associated with only a modest decrease in maternal RNA copy number, and that reduction in RNA level by ZDV explained only part of the observed treatment effect. Other studies have suggested that the presence of autologous or broadly reactive neutralizing antibody in HIV-infected women may be associated with lower rates of HIV transmission to their infants. An active immune response of

newborn infants to HIV has also been suggested to be effective in averting perinatal transmission by studies reporting detection of HIV-specific cellular immune responses in some uninfected infants born to HIV-infected women. Additionally, several investigators have reported the rare occurrence of apparent clearance of HIV infection in perinatally exposed infants.

Thus, vaccines capable of stimulating the mother's and/or infant's immune response or passive immunity therapies may be capable of reducing perinatal transmission. Like hepatitis B, the use of active, passive, or active/passive strategies to reduce transmission has the highest potential for reducing mother-to-child transmission in developing countries.

Clinical studies targeted toward developing active or passive immunization strategies to prevent perinatal HIV transmission were conducted at 49 PACTG sites funded by NIAID and NICHD and 4 NIAID-funded AIDS Vaccine Evaluation Group (AVEG) sites and are being conducted at 1 international site through grant support. HIVIG product and trials support for the passive immunity studies was also provided through NHLBI. The PACTG trial of HIVIG (ACTG 185) was halted because with full implementation of the 076 regimen in a much broader group of pregnant women in that trial the rate of HIV infection dropped to less than 5 percent, thus requiring more than 1,000 mother–infant pairs in each study arm to complete the trial.

Vaccine Clinical Trials

To date the NIAID-supported AVEG has conducted or initiated 29 Phase I and II trials with 19 different candidates.

Significant progress has been made in the evaluation of vaccine candidates developed by manufacturers. For example, all vaccine candidates tested to date in Phase I trials have been shown to be safe and well tolerated. Phase I trials involving HIV-seronegative individuals have shown that (1) the majority of vaccines induce binding antibodies; (2) moderate titers of neutralizing antibody directed toward homologous and heterologous laboratory strains of HIV-1 are produced; (3) neutralization of virus in assays employing standard phytohemagglutinin (PHA)-stimulated blasts has not been detected; and (4) the duration of the neutralizing response in some trials has been maintained for up to 2 years in up to 50 percent of the individuals in the trial. In addition, recent studies testing recombinant poxvirus vaccines, including vaccinia-gp160, canarypox-gp160, and canarypox-*env*, *gag*, protease, with or without a subsequent recombinant gp120 subunit booster vaccine, have been shown to induce strong CD8+ CTL responses in a proportion of the volunteers; those boosted with recombinant env proteins also make neutralizing antibodies to laboratory-adapted HIV isolates and to some primary isolates. Studies of a recombinant canarypox vector with HIV *env*, *gag*, and protease is proposed for testing in Uganda to determine whether individuals of

different genetic backgrounds will respond as well as volunteers in the United States and France. More complex vaccinia and canarypox vectors incorporating portions of *pol* and *nef* are now under study. Peptide vaccine candidates that might provide products for boosting specific immune responses to internal core proteins (gag) and env are under study. In addition, particulate vaccines are of high interest, and the first of these, Ty-p24 VLPs, is being tested parenterally with and without adjuvant and with mucosal administration. Addiional studies are planned with other vaccine candidates for mucosal administration.

Phase II Clinical Trials

NIH is now completing followup of a Phase II trial with gp120 vaccine candidates that enrolled uninfected at-risk individuals. Antibody responses did not differ between higher and lower risk populations, and associated studies found that most participants understood the elements of the trial and did not systematically alter their risk behavior as a result of participation in the trial. A second Phase II trial has begun to further explore the combination of recombinant canarypox (containing genetic copies for *env*, *gag*, protease) and boosting with a different recombinant envelope.

Preparation for Efficacy Trials of HIV Vaccines and Biomedical Prevention

Research required to prepare for clinical evaluations of potential vaccine candidates in efficacy trials is being performed in several domestic and international areas with populations at risk of HIV infection. As candidate vaccines become ready for efficacy trials, it will be important to have identified populations who remain at risk for HIV infection after counseling and risk-reduction measures have been implemented and who are willing to participate in the trials. Characterizing the circulating viral strains and risk factors, learning how to effectively reduce risk behaviors, and gaining the support of the communities (and, as applicable, governments) will take considerable time and effort. In preparation for implementation of efficacy trials, investigators participating in the HIVNET are determining the incidence of HIV in populations such as IDUs, gay/bisexual men, and individuals attending STD clinics, in the United States and several international sites, who may participate in future vaccine trials. In addition, risk behavior and the impact of risk reduction efforts are being assessed. Investigators are obtaining virus from individuals who recently seroconverted to ensure that vaccines genetically match virus strains now circulating. Close collaboration has been established and continues between the HIVNET and the FIC AIDS International Training and Research Program (AITRP) to train local investigators and develop necessary laboratory skills and infrastructure for international vaccine efficacy trials and trials of other interventions. These trials provide opportunities for fundamental research to increase understanding of HIV transmission and disease progression.

NIH also plans to study innovative strategies for prevention or reduction of sexual

and perinatal HIV transmission through the domestic and international epidemiologic and vaccine preparedness cohorts already in place. Using this infrastructure, NIAID-supported investigators are studying prevention strategies, such as STD diagnosis and treatment to reduce susceptibility to and transmission between sexual partners, targeted chemical and mechanical barrier methods, behavioral interventions, methods for reducing perinatal exposure to maternal HIV-infected blood and secretions, and simple relatively inexpensive pharmacologic or immunologic interventions to reduce mother-to-child transmission of HIV.

Additional Basic Research Resources

The NIH supports a program to develop and standardize immunologic and virologic laboratory assessments of AIDS vaccines in primates. In addition, NIH supports an AIDS vaccine reagent project for clinical analysis and preclinical vaccine development.

NIAID supports the AIDS Research Reagent and Reference Program, which provides an extensive repository of materials useful in basic and applied research for vaccine development.

Scientific Issue:

More basic knowledge is needed to define protective immune responses to HIV in order to facilitate the development of vaccines and other biomedical intervention strategies to prevent and control HIV infection.

Objective:

4.A **Increase scientific knowledge of host defense mechanisms leading to protection against HIV infection and disease.**

Strategies:

- Develop and improve animal models that are practical and as much as possible are representative of the spectrum of HIV infections, including use of appropriate HIV cellular receptors, different modes of transmission and development of AIDS; make models amenable to use in evaluating protection by vaccines or other biomedical interventions and, where protection can be demonstrated, in developing new and better assays to determine the correlates of protective immunity;
- Determine the mechanisms of immunologically mediated control of infection with HIV and other related retroviruses, including the role of specific and nonspecific cellular and biochemical immunity in inhibiting viral replication to provide a basis for optimal vaccine design;
- Define the structure–function relationships and the antigenicity and immunogenicity of HIV proteins interacting with CD4, chemokine, and other cellular receptors to improve vaccine designs that will more effectively induce immune responses to block infection by active and passive immunity; define conserved epitopes in which substitutions cannot be tolerated by the virus;
- Define and characterize viral B cell and T cell epitopes that induce protective immunity; understand their structure and antigenicity and determine whether and how their immunogenicity can be exploited in vaccine development;
- Determine how HIV or other lentiviral proteins, particularly glycosylated proteins, are synthesized and how epitopes are selected and presented to the immune system;
- Study immunological memory and long-term protective function of different subsets of human lymphocytes; define factors that favor establishment of memory

cells able to generate effective recall to vaccine antigens and development of long-term protective immunity, particularly in human subjects;

- Gain additional basic knowledge, assay development, and/or reagents to determine
    - Mechanisms of virus neutralization and the reason(s) for the difficulty to neutralize primary isolates;
    - Heterogeneity of specific responses to an immunogen within distinct compartments of the immune system and identification of factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral;
    - Factors that promote development of particular effector cell types, promote production of antiviral substances including chemokines, and enhance non-antigen-specific protective mechanisms;
    - Mechanisms resulting from exposure to HIV that interfere with induction or propagation of vaccine-induced effector responses;
    - Basis for immune reactivity (both humoral and cellular) across divergent HIV types (clades and biotypes); and
    - Mechanisms by which certain HIV immune responses can contribute to immunodeficiency or enhancement of viral replication;
- Study acutely infected individuals, exposed/uninfected or possibly transiently infected humans (and other primates), and nonprogressors to define early immune responses and potential vaccine-inducible host immune responses and viral factors (or viral attenuations) that reduce the amounts of circulating virus and impact disease course; ensure that plasma, peripheral blood mononuclear cells (PBMC), biopsy, autopsy, and other key patient and animal samples, including CNS samples and derived cell lines, are accessible to qualified laboratories;
- Understand how and why HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response; design vaccine approaches to prevent this;
- Determine how infection with one strain of HIV or related lentivirus confers protection against subsequent infection or viral replication of a second virus strain; determine the protective mechanism, duration, and extent of crossprotection;
- Explore strategies to elucidate the important mechanisms for protective immunity against HIV, including amplification of selected responses by passive transfer of antibody or immune cells and subtraction by deletion of selected components of the immune system in primate models;

- Study chronic infection with attenuated viruses, such as SIV variants shown to protect macaques against virulent SIV strains, to understand what properties of the virus and the immune system are responsible for lack of disease induction and protection from challenge with wild-type virus;
- Study mucosal immunity to viral and microbial antigens in animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission;
- Develop or improve sensitive quantitative measures of HIV (and SIV) concentration in bodily fluids to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression;
- Determine the effect of intercurrent STDs or therapy on viral shedding in vaccinated subjects; model these questions in primates;
- Study mechanism of action of vaccine adjuvants and enhanced modes of antigen presentation to induce different cytokine responses; carry out translational research in primates and humans; and
- Explore the molecular epidemiology, humoral, and cell-mediated immune response to HIV-1; acquire clinical specimens from populations relevant to vaccine trials for scientific analyses; and acquire appropriate epidemiological information to assist in interpretation of these analyses.

Scientific Issue:

The identification of viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates will facilitate development of effective vaccines.

Objective:

4.B **Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in preclinical (laboratory studies and animal models), and foster collaboration with industry in the research and development of candidate vaccines.**

Strategies:

- Support the design and development of potential vaccines, including vaccines composed of the following:
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - Whole-killed HIV and safer genetically engineered, noninfectious HIV mutant virions that lack the viral RNA genome or have a defect in a critical gene necessary for replication but contain an array of HIV genes for expression of antigenic proteins or peptides;
    - DNA coding for viral proteins;
    - Virus-like particles containing one or more virus proteins or peptides;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins;
    - Recombinant HIV viral protein subunits;
    - Structurally constrained protein fragments and/or peptides capable of inducing and boosting cellular or humoral immunity to HIV;
    - Agents that stimulate or modulate mucosal immune responses or other host defenses including cytokines or chemokines;

- A combination of the above agents and preparations; and
- Other novel agents and preparations;

- Evaluate the efficacy of vaccine and other prevention strategies in animal models of HIV and related lentiviruses by
  - Testing vaccine and other biomedical prevention strategies in animal models that most closely mimic the HIV infection in humans, which might require development of an appropriate model to evaluate coinfection with STDs at the time of virus challenge or administration of drugs of abuse during the vaccination or challenge phase;
  - Determining *in vitro* correlates of an *in vivo* protective immune response;
  - Determining the effect of vaccine formulation and regimen as well as the nature, timing, and route of infectious virus challenge on the characteristics and effectiveness of the vaccine-induced immune response;
  - Defining the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, disease progression, and biologic characteristics of breakthrough virus including transmissibility;
  - Designing and conducting comparative studies to evaluate of novel vaccine approaches;
  - Conducting long-term followup of vaccinated animals that become chronically infected to determine the impact of vaccination on disease progression whenever possible;
  - Studying the effect of viral mutation and escape on the efficacy of the immune response; and
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization and to infection;

- Support design and development of methods to improve or modulate immune responses (qualitatively or quantitatively), including
  - Novel adjuvants and presentation methods that might enhance effective dendritic cell antigen presentation;
  - Vaccines incorporating cytokines (or their genes in vectors) or other biologically active molecules; and
  - Other novel strategies including nutritional supplementation that might have an impact on vaccine responses;

- Encourage development of candidate vaccines of suitable genetic and antigenic types and possessing stability and route of administration characteristics appropriate for foreign as well as domestic use;
- Develop bacterial and viral vaccine vectors for diverse HIV viral antigen expression and vectors that might provide dual benefit for HIV and some other pathogen;
- Support development of reagents and methods to better assess immune responses in macaques and humans, especially for both humoral and cellular aspects of systemic and mucosal immunity;
- Develop better *in vitro* methodologies to measure immune responses to primary viral isolates;
- Characterize and evaluate the potential negative side effects of candidate vaccine designs, including the potential to increase the frequency of infection or the rate of disease progression in animal models;
- Encourage linkage of academic investigators and industry sponsors to produce pilot lots; investigate novel vaccine design concepts in primate animal models; and
- Develop infrastructure; address scientific, legal, and regulatory issues to foster and encourage participation by, and collaboration with, industry and other agencies in the research, development, production, and clinical testing of candidate vaccines.

Scientific Issue:

Distinct study designs and vaccine or intervention strategies are needed to achieve protection of newborns and infants because of the unique nature of their immune responses and modes of exposure to HIV.

Objective:

4.C **Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of safe and effective active and passive vaccine strategies for preventing or controlling HIV infection in both domestic and foreign pediatric populations.**

Strategies:

- Develop animal models of maternal-fetal and maternal-infant perinatal transmission that can
    - Determine correlates of protective immunity;
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants in relevant animal models (particularly primates);
    - Determine safety of various monoclonal and polyclonal antibody preparations in relevant animal models;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal transmission in relevant animal models; determine whether there is attenuation of disease progression among those neonatal animals that become infected despite immune intervention; and
    - Evaluate the effect of antiviral drugs in combination with immune prevention strategies;
- Determine virologic and nonimmunologic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for, or the design of an HIV vaccine or immune-based intervention for perinatal transmission:
    - Determine the importance of viral load and viral phenotypes (or biotypes) and genotypes in perinatal HIV transmission;

- Develop standardized methods to detect, characterize, and quantify HIV in cervico-vaginal secretions to determine their potential relevance in perinatal transmission;
- Determine if virus in maternal genital secretions is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant; and
- Determine if subtypes of HIV differ in their perinatal transmissibility and what factors are associated with such differences;

- Determine immunologic factors that influence transmission of HIV-1 from mother to infant:
  - Seek to identify maternal and infant immune responses that might prevent transmission to infants;
  - Evaluate the importance of maternal/newborn humoral immune response in transmission and establishment of infection; and
  - Evaluate the importance of the maternal/newborn cellular immune response in transmission;
- Determine specific immune strategies for perinatal intervention to block interaction of HIV with its receptors and coreceptors;
- Develop and maintain domestic and foreign trial sites necessary to enroll mothers and infants in prospective long-term followup trials of vaccines, passive immunity, and other perinatal interventions, which should include both the assessment of duration of detectable humoral immune responses as well as memory or recall responses in the cellular immunity compartment;
- Characterize the transmitted viral subtypes and changes that are occurring in proposed trial sites; evaluate the impact that genetic polymorphisms in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness;
- Develop criteria to define infant infection status as a perinatal intervention trial endpoint in countries where breast-feeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, and length of followup;
- Establish criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations into Phase I, Phase II, and Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children;

- Select and evaluate the safety and immunogenicity (or pharmacokinetics) of various HIV vaccines, adjuvants, vaccine administration regimens, and passive antibody preparations among
    - HIV-infected pregnant women and
    - Newborns with HIV exposure (born to HIV-infected women);
- Conduct Phase I, Phase II, and Phase III clinical trials of the most promising candidate vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or HIV-exposed children;
- Study viral isolates from infants (and their mothers) who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus;
- Study the immune responses of infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the quality and quantity of the infected infant's antiviral responses; and
- Study the impact of early antiviral therapy on the antiviral immune responses of HIV-infected infants.

Scientific Issue:

Suitable candidate vaccines need to be selected, developed, and evaluated in Phase I and Phase II trials to determine safety and immunogenicity.

Objective:

4.D **Select candidate vaccines or concepts suitable for Phase I and Phase II trials, and conduct these trials.**

Strategies:

- Support the conduct of Phase I and Phase II coordinated clinical trials that will determine long-term and short-term safety and compare immunologic responses to preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters;
- Develop a mechanism to evaluate the suitability of vaccine candidates and facilitate entry into Phase I and Phase II trials—animal model data should be included in the evaluation criteria;
- Develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I and II trials that would facilitate broader participation;
- Design and conduct Phase II trials using promising HIV vaccines that are also genetically or immunologically related to HIV isolates circulating in the proposed trial population—trials should address questions that test vaccine concepts and be of an appropriate size to provide data on the frequency of immune responses to facilitate decisions regarding initiation of efficacy trials;
- Isolate and characterize virus and follow clinical course and immune responses of vaccinees who become HIV-infected; study viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses;

- Conduct behavioral research particularly on Phase II trial participants to establish whether their risk behavior has been influenced by participation in a vaccine trial, with emphasis on individuals who become infected while participating; and
- Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

Scientific Issue:

Preparation for HIV vaccine efficacy trials requires characterization of the biological and behavioral factors in affected populations, including seroincidence, and development of trial site infrastructure, including a series of studies and planning activities to ensure trial feasibility.

Objective:

4.E **Identify and maintain appropriate domestic and foreign populations, and develop strategies, infrastructure, and collaborations with government, communities, and industry necessary for ensuring adequate performance of efficacy trials, while balancing the prevention needs of the at-risk populations.**

Strategies:

- Develop potential domestic and foreign sites with access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible;
- Develop and maintain the necessary laboratory infrastructure at designated sites for conducting domestic and foreign vaccine efficacy trials;
- Establish linkages with communities or community organizations where efficacy trials might be conducted to optimize education, recruitment, and followup activities and to help address community concerns, resolve social issues, and ensure ethical conduct of AIDS vaccine efficacy trials;
- For international trials, work closely with national (host) governmental and regulatory authorities, collaborating institutions, vaccine manufacturer(s), and UNAIDS to prepare for, plan, and conduct vaccine efficacy trials adhering to the highest ethical and scientific standards;
- Carry out appropriate epidemiologic studies that determine and monitor changes in the risk profiles and infection rates (seroincidence) of various populations in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and compliant participants in vaccine trials;

- Acquire and analyze HIV isolates from mucosal as well as systemic compartments from recent seroconverters representative of potential efficacy trial populations so that genetic and antigenic information about virus circulating in the population can be obtained;
- Explore innovative trial designs to improve efficiency of vaccine efficacy studies; e.g., determine the impact of HIV vaccines on viral load and risk of subsequent transmission in vaccinated individuals who become infected after administration of the trial vaccine, utilizing discordant couples;
- Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; assess their potential impact on the evaluation of vaccine efficacy;
- Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials;
- Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm;
- Determine optimal methods of achieving informed consent for vaccine efficacy trials;
- Prepare for adequate long-term followup of individuals participating in vaccine clinical trials, where it will be necessary to determine the longevity of immune response, the correlates of immune protection, long-term safety, the impact of participation on risk-taking behavior, and the possible positive or negative effects of vaccine immunization against disease progression and HIV transmission; and
- Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities including research on TB and STDs; integrate research on vaccines against OIs as appropriate.

Scientific Issue:

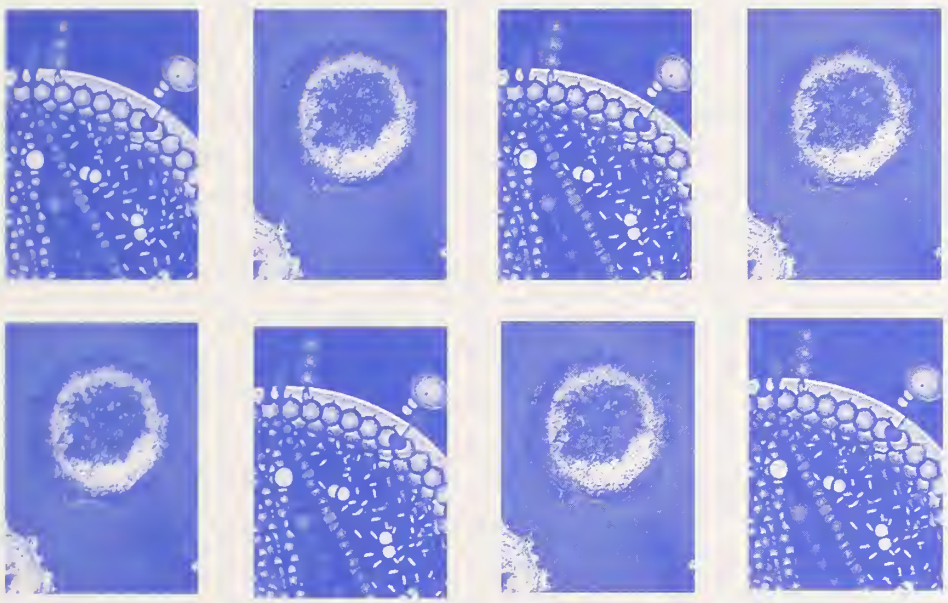
Conduct HIV vaccine efficacy trials of the most promising candidate vaccines in well-characterized, high-risk populations to identify effective vaccines for the control of HIV infection.

Objective:

4.F **Select suitable vaccine candidates, and support efficacy trials when appropriate criteria are met.**

Strategies:

- Establish criteria with concurrence of an advisory group that has the requisite scientific, public health, Government, and community expertise; and
- Conduct large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria:
    - Evaluate HIV vaccine candidate efficacy against infection, disease, and/or transmission;
    - Evaluate additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity; and
    - Ensure that trials are conducted with the highest regard for social and ethical standards.



Behavioral and Social Science Research

AREA OF EMPHASIS:

Behavioral and Social Science Research

Status:

At present, the most effective way to prevent or reduce the spread of HIV/AIDS is through behavioral change. The majority of AIDS cases in the United States and globally result from two activities: unprotected sexual intercourse with an HIV-infected person and the use of HIV-contaminated injection drug equipment. The primary goal of NIH-sponsored AIDS-related behavioral and social science research is to discover how to change the behaviors that lead to HIV transmission—including preventing their initiation—and how to maintain protective behaviors once they are adopted. An additional goal is to reduce the negative impact of HIV on individuals with HIV infection, their families, the health care system, and society.

Current research priorities in the behavioral and social sciences reflect recent and significant developments. First, the development of new and more effective drug therapies—in particular combination therapies—for combating HIV infection has raised a host of behavioral questions that have significant implications for HIV prevention and treatment. With combination therapies, the number of drugs and frequency of dosing require strict adherence to regimens that may be difficult for many people to achieve. Lack of complete adherence may result in the development of resistant strains of HIV, which could have devastating implications for our ability to stem transmission and treat HIV-infected individuals. In addition, as HIV-infected individuals experience improved health and a decline in detectable virus in their body as a result of taking the new combination therapies, they may come to believe they are less infectious and may lapse into unsafe sexual and drug-using behaviors. This could have the effect of increasing HIV transmission, if the virus is still viable at undetectable levels. These issues highlight the importance of research on how best to ensure adherence to both pharmacological and behavioral HIV-related interventions.

A second major development is the recognition that large-scale HIV prevention strategies adopted by national and local governments have been effective in reducing transmission in a number of countries and cities. Policy changes related to promoting access to and utilization of known HIV prevention measures, including condoms, sterile injection equipment, and delaying or abstaining from sexual intercourse, have resulted in documented declines in HIV incidence even in high seroprevalence countries, such as Thailand and Uganda. This suggests the need to further study the impact of legal and policy changes on stemming the AIDS epidemic through behavioral change, both domestically and internationally.

With these recent developments in mind, the NIH sponsors research related to the following: developing, implementing, and

evaluating behavioral and social interventions to reduce HIV transmission; strengthening our understanding of the determinants, trends, and processes of HIV-related risk behaviors and the consequences of HIV infection; developing and evaluating behavioral strategies for preventing or ameliorating the negative physical, psychological, and social consequences of HIV infection; and improving the research methodologies employed in behavioral and social science research. The idea that HIV-related behavior and behavior change must be viewed within a human developmental framework cuts across these issues. Accordingly, research must address emerging issues at different points along the developmental trajectory from childhood through old age, including middle childhood, adolescence, young adulthood, and middle age. Also cutting across priorities in the behavioral and social sciences is a continued commitment to fostering better linkages among researchers, communities most affected by HIV and AIDS, and organizations responsible for providing HIV prevention and health care services.

Rapid advancement of meaningful and effective HIV-related behavioral and social science research requires further development of methodological tools. As with other areas of HIV research, methodology represents the essential building blocks of HIV-related behavioral and social science research, and, therefore, it must be given special attention at NIH to facilitate rapid advancement of both basic and intervention research.

Interventions To Prevent HIV Transmission

In the past 15 years, much has been learned and accomplished in the area of HIV/AIDS prevention through behavioral change interventions. Theory-driven intervention models have been developed and employed by researchers supported by NIH and have demonstrated that preventive interventions work even among "hard-to-reach" and socially disenfranchised populations. These interventions have resulted in marked changes in the sexual and drug-using behaviors most implicated in HIV transmission (i.e., engaging in unprotected sexual intercourse and sharing unsterile drug injection equipment) among such groups as rural gay men, out-of-treatment IDUs, homeless and runaway youth, and the seriously mentally ill.

For example, NIH-supported research has demonstrated that multifaceted risk-reduction programs (including drug treatment, outreach and education on HIV risk, and provision of sterile injection equipment) can produce significant and sustained decreases in HIV risk behavior among IDUs, even among those who continue their drug abuse. Numerous studies have documented that drug abuse treatment, particularly methadone maintenance programs, significantly reduce needle-related risk behaviors, such as frequency of drug injection. These behavioral changes are consistent with seroprevalence and seroincidence data indicating reduced risk of HIV transmission. Studies of outreach strategies for out-

of-treatment IDUs also have demonstrated significant levels of behavioral change. A recent summary of NIH-supported studies in 12 cities documents the effectiveness of HIV risk-reduction education in reducing drug injecting and multiperson use of syringes and other drug injection equipment. Other studies have shown a relationship between the use of sterile syringes obtained through needle exchange programs or pharmacy sales and reductions in needle sharing.

Delaying the initiation of sexual intercourse and dissuading youth from engaging in drug use also have been important HIV prevention strategies developed and tested by NIH-supported researchers. In one study, 89 percent of abstinent youth who received HIV information and a skills-training intervention delayed initiation of sexual activity for 1 year postintervention, compared with 68 percent of those who received only the HIV information.

To date, most behavioral change interventions have been tested in small groups, in a limited number of communities, and over relatively short periods of time (6- to 12-month followup periods). It is now important to replicate and refine the most successful of these interventions to test their effectiveness on a broader scale and over longer periods of time, and to develop new interventions to address behaviors that have proven most resistant to change. More data should be collected on high-risk behaviors and seroconversions in cohort studies to permit better modeling of HIV. Where appropriate, interventions should be tested in randomized, controlled trials, and, when possible, HIV seroincidence should be an additional outcome measure. NIH-supported researchers are engaged in multisite investigations to identify the most effective components of behavioral interventions for different populations, including IDUs, crack cocaine users, and primary health care and STD clinic patients, and to assess their effect on both behavioral change and STD and HIV seroincidence in those populations. In addition, determining the cost-effectiveness and cost-utility of such interventions is an area of current exploration by NIH-supported researchers.

Research has demonstrated that, in order to be successful, preventive interventions should be tailored to specific populations and must take into account the cultural and social contexts of different people's lives. NIH-supported projects informed by theoretical models from the behavioral and social sciences are uncovering the specific elements of social and cultural life that contribute to HIV risk and protective behaviors and that must be addressed in interventions. For example, one study investigated how different personal and social resources, threat appraisal processes, and coping styles affected the differential use of condoms among homeless African-American and Latina women and concluded that culture-specific strategies that attend to these differences are necessary to effect positive behavioral change among these women.

Community-level interventions may be an important way to effect behavioral change

on a broad scale. NIH-supported researchers have investigated the impact of community-level approaches both in the United States and abroad. For example, in a study of five cities in which HIV had entered a heterosexual IDU community but where HIV seroprevalence remained low and stable, three common prevention components were identified: beginning prevention early; community outreach; and access to sterile injection equipment. The researchers concluded that in low seroprevalence areas, such community-level approaches may limit transmission of HIV among populations of IDUs despite continuing risk behavior among a substantial proportion of the population.

Other important areas of intervention research at NIH include the following: the acceptability of both biomedical and behavioral interventions among different individuals and communities; the behavioral aspects of the adoption of new HIV prevention technologies, such as the female condom, microbicides, or the use of ZDV by pregnant women to prevent vertical transmission of HIV; and social and psychological factors influencing participation in study trials and adherence to medical regimens for the treatment of HIV- and AIDS-associated disorders.

Understanding HIV Transmission

Ensuring the relevance and effectiveness of behavioral change interventions for HIV prevention requires understanding the psychological, social, and cultural factors that contribute to HIV risk and protective behavior. Specifically, in the area of HIV and AIDS, NIH-supported researchers are investigating the mechanisms that influence risk behaviors—from neurobiological factors related to sexual drive and drug addiction to psychological factors related to self-esteem and the ability to negotiate safe sex to social and cultural factors related to laws, norms, and values about sexuality, drug and alcohol use, and HIV/AIDS itself. This basic research, including the development and testing of theories of behavioral change and maintenance in the context of HIV risk, is the essential underpinning of primary prevention and early intervention efforts.

Studies of decision-making processes have identified psychological factors, knowledge, attitudes, and behavioral intentions as important in leading to behavioral change among individuals. Most of these approaches focus on the individual at one point in time or stage of life. However, HIV risk and behavioral change may be experienced differently by people at different stages of development and different points in their lives. This suggests the importance of including a developmental and a life-course perspective in HIV prevention and intervention research.

Moreover, it has become apparent that the social nature of HIV risk behavior requires a broader focus than merely on the individual. NIH-supported research has demonstrated the significance of partners, social networks, families, and peer groups in influencing an individual's engagement in or avoidance of risk behavior. For adoles-

cents, research has determined the important role both parents and peers play in decisions to initiate or postpone sexual activity. For example, in a study of inner-city youth, simply having the parents monitor the adolescents' activities was associated with a delay in sexual initiation. The dynamics of relationships play a central role in influencing protective behaviors. Studies show that adolescent males' use of condoms declines the longer they remain with a given partner. One study demonstrated that an intervention that helped women develop negotiation skills was very effective with new partners, but was less so with ongoing partners.

Personal networks have been determined to be both sources of HIV transmission and potential targets of HIV preventive interventions. In one study among IDUs, for example, researchers found that higher total personal network density and larger drug network size were positively associated with needle sharing. Another study of sexual networks demonstrated that individuals who had partnerships that overlapped in time had 5 times the risk for HIV infection than those who practiced serial monogamy. Understanding the characteristics and dynamics of networks has led to interventions that interrupt such risky practices.

Another area of particular importance for understanding HIV transmission is the overlap in HIV-related risk behaviors. NIH-supported researchers are investigating the complex interplay of alcohol use, drug use, and poor impulse control and their impact on risky sexual behavior, including the situational factors that contribute to their mix. For example, one study determined that partner characteristic (steady, long-term versus casual) moderated the relationship between alcohol use and high-risk sexual behavior among gay men. Individuals without steady partners were 4 times more likely to engage in risky sex (unprotected intercourse) under the influence of alcohol than those with steady partners.

Consequences of HIV Infection and AIDS

Despite progress in prevention and treatment of HIV disease, AIDS will continue to have a significant impact on individuals and communities both domestically and globally. NIH-supported researchers have been studying the consequences of HIV and AIDS on individuals, their loved ones, and caregivers for some time now. These investigations span the sciences from neuroimmunology to social psychology, as they address such issues as the bidirectional relationship between stress, depression, and immune functioning in individuals, the psychological costs and benefits of caregiving, and the impact of bereavement on individuals' mental health.

Because the AIDS epidemic has a devastating impact on families and communities, it has become increasingly important to investigate its social and cultural consequences. For example, NIH-supported researchers are examining the implications of the "stigma" of HIV/AIDS—that is, as a disease that is generally fatal and whose transmission is characterized primarily by socially marginalized activities—on the care and

treatment of infected persons; the social and psychological status of orphaned children whose parents have died from AIDS; and the impact of HIV/AIDS on health care systems and economies of communities that have been most affected by the epidemic.

Research and Evaluation Methodologies

As advances in the range and type of research questions being addressed are made, so are advances in the methods being employed to answer them. Over the past 15 years, significant improvements have been made in enhancing data collection. Advances and refinements of qualitative and quantitative methods for gathering information, e.g., computer-assisted survey instruments, have improved both the collection and the confidentiality of data, including self-reported data. Some NIH-supported studies are collecting micro-biological and disease outcome data (e.g., STD and HIV serological test results) as an additional measure to use in conjunction with self-reports. Laboratory tests have improved for detecting STDs and HIV and the collection of specimens in the field has improved (e.g., through saliva tests for HIV and improved urine collection bottles). These developments were recently applied for the first time in a nationally representative study of sexual risk and protective behaviors among adolescent and young adult men.

Some behavioral change interventions have been developed to the point where they now can be tested in quasi-experimental or randomized controlled trial designs to better ascertain their effectiveness. One such NIH-supported multisite, randomized, controlled study is testing the efficacy of a cognitive-behavioral intervention using both self-reported behavioral change and STD incidence as outcome measures. In addition to behavioral change and STD outcomes, HIV seroincidence data are also being collected as an intervention outcome measure in a number of studies.

Additionally, new techniques for improving our ability to quantitatively estimate the success of behavioral interventions in preventing the spread of HIV are being developed by researchers with expertise in mathematical modeling and biostatistics. For example, NIH-supported researchers have developed models to estimate the number of HIV infections averted through the implementation of a one-for-one sterile needle exchange program and to estimate how effective a vaccine program would be in stemming the rate of HIV transmission in one city given various scenarios related to the level of vaccine efficacy, use of the vaccine, and behavioral change. Continued support over the next few years should see further refinement in such methodologies that will produce better estimates for projecting the course of the AIDS epidemic in different regions and populations and the possibilities for stemming it through specific interventions. In turn, this will improve our ability to determine which interventions are successful and which are not and to apply resources accordingly.

The evaluation of HIV prevention strategies and programs is a vital part of the behavioral and social science agenda at NIH. Conducting successful evaluation—both program evaluation and cost-effectiveness/cost-utility evaluation—requires sophisticated methods, including the identification and perationalization of appropriate outcome measures. Further development of methods in this area will allow us to determine not only which interventions are most successful, but also whether particular components of interventions are more effective than others.

Scientific Issue:

HIV prevention interventions have demonstrated that HIV-related risk behaviors can be measured and modified. As the epidemic evolves, effective strategies are required for reducing HIV transmission for many populations not yet reached by these interventions. In addition, maintenance of intervention effects, including the demonstration of their impact on HIV seroincidence, is a priority. Research has demonstrated that drug abuse treatment, outreach and counseling, and syringe availability programs reduce risk of HIV infection among injection drug users; however, further development of comprehensive interventions that address the combination of drug use and sexual risks is required. Finally, efforts must be expanded to integrate interventions at multiple levels of influence and to use multiple methodologies and outcomes to validate their effects.

Objective:

5.A **Support research to develop, evaluate, and diffuse social and behavioral interventions at the societal, community, organizational, social network, dyadic, and individual levels to reduce HIV transmission by reducing HIV-related risk behaviors and increasing protective behaviors. Multisite, cross-national, and international studies are encouraged.**

Strategies:

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions in different domestic and international settings and populations to reduce high-risk HIV-related sex and drug use behaviors and HIV transmission.

(Populations and Contexts)

- Develop and test interventions targeted at HIV-infected persons to reduce their risky sexual and drug use behaviors;
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission;

- Support intervention research to enhance healthy sexual development and responsible protective behaviors (including access to and use of barrier methods, avoidance of too-early or nonconsensual sex, and abstinence from unsafe sexual behavior) throughout one's lifetime;
- Support interventions for populations that are currently low risk or that perceive themselves to be low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors, e.g., non-sexually active, non-drug-using adolescents; heterosexual men and women; middle-aged and older populations;
- Develop, test, and evaluate interventions that target individuals returning to society from the prison system—strategies include increasing access to education, information, therapeutic care, prevention services, and clinical trials; and
- Support the capacity to develop rapid-response intervention studies.

(Effectiveness)

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization—individual, dyad, family, network, community, institution, and society—and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts;
- Support research to increase the effectiveness, cost-effectiveness, and cost-utility of HIV-related drug abuse, mental health, alcoholism treatment, and family planning interventions—such research may include the development of new pharmaco-therapies and behavioral therapies to reduce HIV-related risk behavior and HIV transmission in different settings and populations;
- Support research in the United States and abroad to improve the transfer of effective HIV interventions to and from the community; support research on the adoption and adaptation of efficacious HIV interventions by communities (including studies of diffusion processes and the exchange of knowledge between service providers and researchers)—this includes research on the maintenance of effective interventions as well as assessing the generalizability of interventions with diverse populations; and
- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.

(Systems)

- Support research that investigates the impact of laws and policies on HIV transmission;

- Support research to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, family planning, and social services that reduce HIV risk behaviors and HIV transmission;
- Support research to understand and improve linkage, coordination, and integration among primary medical care, drug, alcohol, and mental health treatment, STD treatment, reproductive health and family planning services, social services, and community-based HIV prevention services;
- Support research to integrate HIV risk-reduction goals and assessments into existent models of drug abuse treatment, e.g., methadone maintenance, outpatient drug-free, inpatient, and therapeutic community treatment programs; and
- Support intervention research on strategies for changing the willingness of communities to support and adopt primary prevention interventions.

(Methods)

- Design and test behavioral interventions to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials for prophylactic vaccines, microbicides, and other biomedical prevention methods;
- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in HIV preventive intervention research; and
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.

Scientific Issue:

Recent years have witnessed important changes in HIV treatment. At the same time, however, the AIDS epidemic has spread to new and different populations. Understanding the implications of these two developments requires basic behavioral and social science research focused on HIV-infected individuals and on populations likely to become infected with HIV. Research is needed to understand the antecedents and consequences of risk and protective behaviors at the societal, community, organizational, network, dyadical, familial, and individual levels. Additional basic research is needed to identify the behavioral, psychological, cognitive, and social factors that affect HIV treatment and disease management. Models based on this understanding should be developed for guiding interventions to prevent the transmission of HIV and to reduce its adverse consequences. Further research on the improvement of methodologies to address fundamental issues in the prevention and the consequences of HIV is also needed.

Objective:

5.B **Support basic social and behavioral research to strengthen understanding of the determinants and processes influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes research that examines the societal, community, organizational, social network, dyadic, and individual barriers to the utilization of effective preventive and treatment interventions.**

(The scientific objectives 5.B and 5.C are of equal weight.)

Strategies:

(Emerging Priorities)

- Conduct basic research to better understand the impact of HIV therapeutic regimens on adherence, sexual risk behaviors, and psychosocial adaptation; and

- Develop new models of behavioral change that integrate biological, psychological, and social perspectives to explain and predict the acquisition and maintenance of HIV-related behaviors among vulnerable individuals and understudied groups; support theory-building studies developed in the context of HIV prevention research (rather than simply adapted from other health science domains), including studies that adopt a developmental and life-course perspective.

(Consequences)

- Support research on the decision-making processes of health care workers regarding the offering of HIV counseling and testing and other prevention services and the prescription of HIV-disease treatments;
- Conduct research on children affected by HIV, including early identification and assessment;
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities;
- Support research on the economic and social implications for retired and older individuals who provide support and care to younger family members or friends with HIV/AIDS and their dependents;
- Support interdisciplinary research, involving behavioral and biomedical scientists, to determine whether a bidirectional relationship between stress, depression, immune system functioning, and HIV infection exists and, if so, to examine the psychosocial and physiological factors affecting that relationship; and
- Support studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research, employing animal models, to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure upon social behaviors (e.g., mother-infant attachment, peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

(Prevention)

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities; study how HIV risk might change over time

as a function of developmental and life-course events, such as childbearing, marriage, divorce and separation, and aging;

- Conduct research on decision-making processes that relate to sexual and drug-related risk-taking across the life-course, e.g., individual and dyadic decision processes concerning whether and under what circumstances to have sexual intercourse; risk assessment of self and partner; adjudication of pregnancy prevention, HIV prevention, and relationship goals in choosing to use a condom and/or other method; and decision processes related to sharing needles and having sex with someone who may be infected;
- Support multidisciplinary research that investigates the biobehavioral and sociobehavioral determinants and mechanisms of sexuality, including processes of sexual and gender identity formation;
- Conduct research on partner selection and relationship dynamics, including studies of how partner choice, partner formation, relationship development, and partner stability change over the life-course and affect health-related behavior—studies should examine psychological, cultural, and social factors that influence these phenomena;
- Support multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission—such research may also include studies that investigate the relationship between any drug use and sexual risk behaviors;
- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV—such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships;
- Study the social, structural, cultural, and demographic factors, such as socioeconomic status, marital status, ethnicity, sexual identification, age, and gender, that influence HIV-related behavior across the life-course, affect access and delivery of care—including cost-effectiveness and cost-utility of behavioral change interventions—and influence the implementation of intervention strategies;
- Support research to understand how and whether communities engage in HIV preventive interventions; determine how to better ensure the use of prevention research by communities, public health entities, and policy planners in the United States and abroad;

- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention and treatment interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics;
- Support behavioral and social research on the acceptability and use of biomedical HIV prevention methods (e.g., condoms, microbicides, and vaccines); and
- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.

Scientific Issue:

Advances in therapy for HIV mean that infected individuals need access to treatment strategies for coping with HIV disease and for enhancing quality of life. Research is needed on interventions to improve treatment adherence and to ameliorate negative physical, behavioral, psychological, cognitive, and social consequences of HIV infection. Research also is needed to improve delivery of care and access to therapeutics among diverse population groups. Qualitative and quantitative research methodologies should be further developed to address these adherence, quality-of-life, and health care delivery issues.

Objective:

5.C **Support research for the development, evaluation, and diffusion of strategies to improve treatment adherence and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV, including stigmatization of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among all persons with HIV infection.**

(The scientific objectives 5.B and 5.C are of equal weight.)

Strategies:

(Treatment and Care)

- Support research on adherence to treatment regimens, including communication techniques to improve shared decision-making between health care providers and HIV-infected individuals, and behavioral strategies to manage symptoms secondary to treatment protocols;
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection, including access, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health-care-

seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age);

- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations;
- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care; and
- Support research to foster more effective participation in treatment planning, decision-making, and formulating advanced directives by patients and families.

(Biopsychosocial Consequences)

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations to cope with HIV infections, maintain quality of life, and avoid engaging in HIV-related risk behaviors;
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection;
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including decisions regarding treatment and quality of life;
- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout; and
- Support research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.

Scientific Issue:

Behavioral and social science research has greatly enhanced our understanding of HIV transmission, the consequences of HIV infection, and health maintenance among HIV-infected individuals. However, a significant commitment must be made to accelerate development of methodologies that will further advance our understanding of HIV-related behaviors and behavioral change; the linkages between HIV-related risk behaviors, HIV transmission, and disease progression; and the evaluation of interventions. Additional research is needed to develop, characterize, and evaluate methods for basic and applied research on HIV-related behavior and associated outcomes.

Objective:

5.D **Support research to advance innovative quantitative and qualitative methodologies to enhance HIV-related behavioral and social science research.**

Strategies:

(Measurement)

- Develop improved methodologies—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS;
- Develop and strengthen culturally, linguistically, and age-sensitive and appropriate research instruments for subpopulations (e.g., HIV-infected children, elderly, prisoners);
- Develop and refine techniques for measuring social networks associated with HIV transmission;
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use: self-report

measures, HIV infection, and other disease outcomes such as other STDs and blood-borne diseases;

- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and factors that influence behavior and behavioral change, and improved triangulated approaches to integrate, analyze, and develop theories from qualitative and quantitative observations;
- Support research to determine how self-reported outcome measures are affected by "response shift," including the effects of disease progression and treatment on the criteria individuals use to appraise their quality of life, and the impact of interventions on participants' standards for judging their degree of risk, level of skills, and adequacy of support and care;
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention interventions; and
- Develop and refine research techniques for measuring responses by organizations to HIV and for characterizing organizations working in the HIV field.

(Modeling)

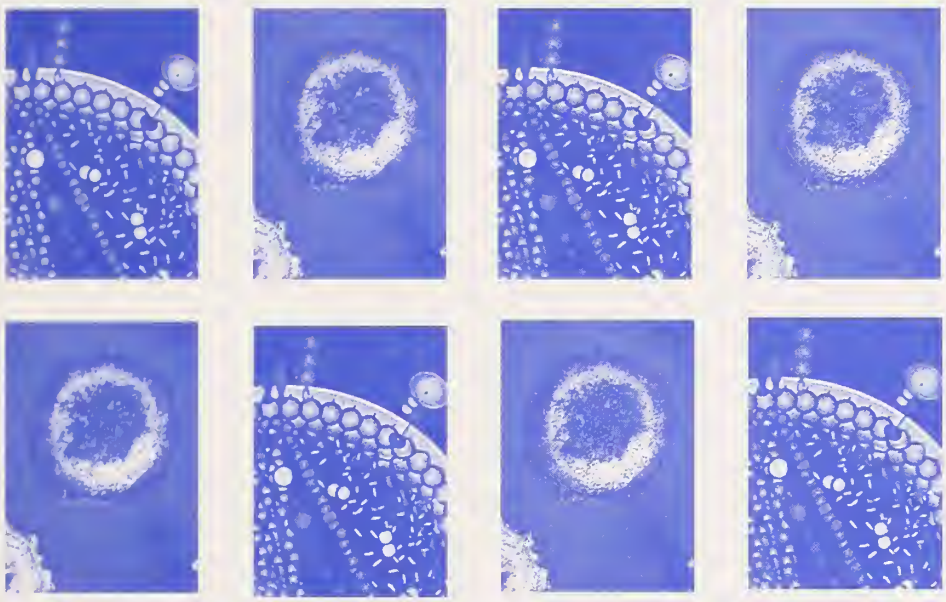
- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence; and
- Improve methods for forecasting and modeling the AIDS caseload, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs.

(Design and Statistical Analysis)

- Develop improved sampling strategies for subpopulations (e.g., children, elderly, gay men of color);
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and -infected populations, including improved followup methodologies, methods to increase followup rates, and methods for dealing with subject attrition, missing data, and non-normal distributions; and
- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of intervention strategies at the individual, group, and community levels.

(Ethics and Other Issues)

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among adolescents, children, psychiatric populations, prisoners, immigrants, and other vulnerable or special populations;
- Develop and refine research techniques to advance multisite, intercultural, and international studies; and
- Encourage secondary data; develop approaches to protect and document confidentiality.



Training, Infrastructure, and Capacity Building

AREA OF EMPHASIS:

Training, Infrastructure, and Capacity Building

Status:

NIH supports several intramural and extramural research resource programs. Included in these programs are grants for training AIDS researchers, supporting animal facilities for animal model research, and constructing or improving existing facilities and equipment for AIDS-related research.

Training Programs

Numerous NIH-funded programs have increased the number of training positions in AIDS-related research. In addition, much of the predoctoral and postdoctoral training supported by NIH from non-AIDS funds provides broad interdisciplinary training that prepares investigators to undertake AIDS-related research. The NIH LRP was mandated by Congress under Public Law 100-607 in 1988 and was authorized under 42 USC 288-1 to encourage health professionals to engage in AIDS-related research at NIH. Twenty-five professionals are currently enrolled. This program continues to attract qualified researchers to NIH.

The FIC sponsors the AITRP, a program for training scientists in developing countries to undertake epidemiologic and postdoctoral research, with the goals of expanding scientific capabilities in the epidemiology, diagnosis, and treatment of HIV/AIDS throughout the world and of facilitating the evaluation of AIDS drugs and vaccines internationally. Established in 1987 at the request of Congress, the program has since provided training in the United States for approximately 1,100 health scientists from 85 countries and supported more than 500 in-country training courses in 50 countries. The program includes an in-country research component, which provides support for reentry grants for scientists returning home after completion of their training, and a Fogarty International Research Collaboration Award (FIRCA) for AIDS. FIRCA provides support for collaboration between U.S. and foreign scientists in the foreign collaborator's laboratory through a grant to a U.S. investigator who is already funded to conduct HIV-related research. OAR Discretionary Funds were provided in FY 1997 to support new and minority investigators through AITRP. This program component is designed to provide overseas research training experiences for U.S. investigators as well, with a special emphasis on new and minority investigators. The FIC investment in research training has facilitated the conduct of many research studies supported by various ICDs.

The NIMH research training program currently fully supports 16 programs that are focused exclusively on issues of HIV infection and AIDS and partially supports 10 other research training programs to allow components of the program to focus on HIV infection and AIDS. These programs have a range of research emphasis including basic behavioral and social science, biopsychosocial and neuropsychological science, prevention and intervention

science, and health services research. In addition, the NIMH AIDS Research Center in San Francisco supports an international scholar training program.

To address the relationship between drug abuse and the spread of HIV, NIDA has taken steps to diversify the expertise of researchers in this area so that future researchers will possess a broad range of biological and behavioral research skills. NIDA's research training program supported 350 predoctoral and postdoctoral investigators through individual and institutional awards in 1996. Spanning basic, clinical, behavioral, and epidemiological research areas, trainees are commonly found in community-based prevention and treatment settings as well as molecular biology or basic neuroscience facilities.

NIH Institutes are adopting innovative approaches to increase the cadre of new investigators in needed research areas, including HIV/AIDS. For example, NIMH and NIDA have a small grants program known as the Behavioral Science Track Award for Rapid Transition (B/START). The B/START program is designed specifically to assist new behavioral scientists in entering the research environment through expedited application and review procedures. While these programs are not limited to HIV/AIDS research, they have provided new behavioral scientists the opportunity to conduct HIV/AIDS studies and collect pilot data that are needed to compete for regular research grants at NIH.

NIAID-sponsored programs increased the number of trainee slots by 121 percent (from 81 to 179 slots) between 1990 and 1995. Recognizing the link between HIV and the reemergence of TB, NIAID initiated a research grant administrative supplement program to encourage young scientists and scientists working in other areas to enter careers in TB and TB-related research. Approximately 10 supplements will be distributed to ongoing research projects in basic and clinical aspects of TB-related research to support scientists new to the field of TB. The research experience is intended to provide opportunities for individuals to develop as independent, competitive research investigators.

Support of Animal Facilities

NCRR and NCI have several successful programs designed to produce primate models for use in the evaluation of potential SIV/HIV vaccines and to ensure adequate supplies of these animals. These programs include the Specific Pathogen-Free Rhesus Breeding and Research Program for the SIV/macaque model system and the successful Chimpanzee Breeding and Research Program (CBRP) for AIDS studies. NCI produces in large scale and maintains the viral stocks for AIDS vaccine trials in chimpanzees. In addition, the Regional Primate Research Centers (RPRC) Program provides specialized facilities, scientific and technical personnel, animal models research and breeding, and a wide variety of nonhuman primate species to

support diverse requirements for AIDS-related research. In FY 1997, NCRR sponsored a special initiative to give non-RPRC investigators greater access to RPRC resources. Development of the SCID mouse model continues for analysis of vaccine candidates and for use in screening potential therapeutics. NHLBI currently supports studies on transfusion-associated HIV infection and AIDS and on the development and evaluation of blood products for the prevention or treatment of HIV/AIDS. The NHLBI Chimpanzee Colony at the Southwest Foundation for Biomedical Research, San Antonio, Texas, has been used to conduct this type of research. Future plans include the use of the colony to evaluate the efficacy of HIV-specific monoclonal antibody preparations.

Intramural and Extramural Research Site Infrastructure

NCRR, through the General Clinical Research Centers (GCRCs), provides research infrastructure for multidisciplinary studies on both children and adults. Specifically, GCRCs provide patient research facilities, computerized data management and analysis, and specialized laboratories as well as research nurses, dietitians, and biostatisticians for the translation of basic and clinical research into medical practice. These facilities support a variety of studies focused on the area of HIV infection and therapy. The NIH-sponsored Research Centers in Minority Institutions (RCMI) program provides for the development of biomedical research infrastructure at minority institutions. Awards previously provided through this program have resulted in the development of infrastructure at three minority institutions, which was necessary for them to successfully compete and receive funding as ACTG clinical trial sites.

Special facilities and equipment are required for the performance of AIDS-related research. NIH has provided funding for the improvement of biomedical research facilities and instrumentation. As part of the plan for improving physical infrastructure at NIH, numerous projects are currently being designed, improved, or constructed for AIDS-related research on the NIH campus.

NIH supports Centers for AIDS Research (CFARs) for the purposes of providing infrastructure and promoting basic, clinical, behavioral, and translational research for all investigators in AIDS and AIDS-related research at institutions that receive significant NIH AIDS funds. In addition, CFARs foster industry collaborations, support minority AIDS scientists, provide AIDS research communications and community outreach, and encourage international collaborations. For FY 1998, there are six NIH Institutes participating in the CFAR program—NIAID, NCI, NIDA, NIMH, NICHD, and NHLBI.

Computers and high-speed computer networks play an increasingly important role in facilitating the understanding of HIV-related pathophysiology at a molecular level and providing rapid communication

among basic and clinical investigators. The NCI Biomedical Supercomputer Center facility was a key resource for the prediction of the secondary structure of the entire 9,433 bases of HIV RNA. NCRR-supported supercomputing centers at Pittsburgh, Illinois, Cornell, and Columbia universities provide similar facilities for investigators nationwide. In addition, NCRR supports several synchrotron and NMR facilities that provide the technology to determine the structure of candidate HIV-related proteins, and NIGMS supports a Protein Data Bank located at Brookhaven National Laboratory, which is a repository for the three-dimensional coordinates of all proteins whose structures have been determined. Specific drugs are being developed on the basis of known molecular structures to block virus action and provide new therapies for HIV infection and its consequences.

A multiagency High Performance Computing and Communications (HPCC) Initiative includes NIH participation by the National Library of Medicine (NLM), the NCRR, the Division of Computer Research and Technology, and NCI. This initiative permits the development of faster computers and better algorithms for predicting molecular structure and function from genetic sequence, which is an important area of research.

The HPCC Initiative will create a National Information Infrastructure (NII) linking academic and commercial research centers. Nearly 10 million users worldwide are connected to the current Internet at this time. NLM provides support for connecting medical centers and community hospitals to the Internet and for developing prototype biomedical digital image libraries that use the Internet as a high-speed distribution channel. NII will provide an increasingly fast communication line for sharing data among laboratories on an international scale.

Repositories play an important role in providing resources for basic science research. NHLBI maintains a repository of blood specimens from individuals with transfusion-associated HIV infection and from AIDS patients who have pulmonary disease. NIAID supports the AIDS Research and Reference Reagent Program, which provides a wide range of reagents such as antibodies, cell lines, recombinant DNA clones, peptides, viruses, and chemicals to investigators worldwide and is one of the World Health Organization's (WHO) AIDS Collaborating Centres. NHLBI and NIAID have established a series of procedural guidelines to increase access to specimens from their cohort and clinical trials by qualified investigators not collaborating in the specific studies supported by these ICDs. In addition, NIAID maintains a centralized repository for specimens from clinical trials and epidemiologic cohort studies. NCI has established and maintains the Tissue and Specimen Bank of HIV-Related Malignancies to provide specimens to qualified investigators studying the pathogenesis of malignancies in HIV-infected individuals.

Scientific Issue:

Meeting the needs of research on HIV/AIDS requires recruiting and training basic, clinical, and behavioral scientists in the United States and abroad in the many disciplines necessary to carry out this diverse scientific agenda. This requirement includes attracting researchers from other scientific disciplines to pursue HIV/AIDS research.

Objective:

6.A **Provide both national and international training in biomedical and behavioral research on HIV.**

Strategies:

- Increase predoctoral and postdoctoral training, as well as advanced research training, in a range of AIDS-related disciplines to a level comparable with that of other training programs within the NIH;
- Provide incentives to attract researchers from other fields to pursue HIV/AIDS research;
- Provide incentives to AIDS-related basic, clinical, and behavioral investigators to foster better linkages across scientific disciplines;
- Increase training to strengthen global capacity to conduct multidisciplinary AIDS-related prevention research in developing countries;
- Support the training of biomedical and behavioral scientists in the use of advanced computer technologies for HIV-related research;
- Expand the NIH AIDS LRP to bring scientists and physicians to the NIH to increase the cadre of trained HIV/AIDS researchers;
- Taking advantage of existing AIDS clinical trials infrastructures, develop specific training programs in clinical trials methodology, including the ethics of clinical research and the design and analysis of observational studies;
- Support training opportunities for HIV prevention researchers interested in adding specific methodological skills to their existing research skills and experience (e.g., methods to conduct cost-effectiveness analyses, measurement of biologic outcomes

in behavioral intervention studies, ethnographic and other qualitative methods, network analysis);

- Target multidisciplinary training with particular emphasis on AIDS-related intervention research such as vaccines, mother-to-child interventions, behavioral interventions, OIs, STDs, microbicides, and clinical trials methodologies;
- Develop and expand programs for AIDS-related research training tailored and targeted to minority researchers, primarily at the postdoctoral level;
- Increase international training and research programs; expand these programs by recruiting trainees from developing countries, with the long-term goal of providing AIDS-related training for leading health scientists; and couple this objective with increased opportunities for trainees to conduct AIDS research in their native country after completion of their training (e.g., providing reentry grants for scientists returning home); and
- Develop new grant mechanisms to link U.S. AIDS research scientists and institutions with each other and with investigators and institutions in both developed and developing countries.

Scientific Issue:

The conduct of HIV research in the United States and abroad requires establishment and maintenance of infrastructure to carry out this research program, including facilities and instrumentation, computers, databases, data communications, laboratories, and animal colonies.

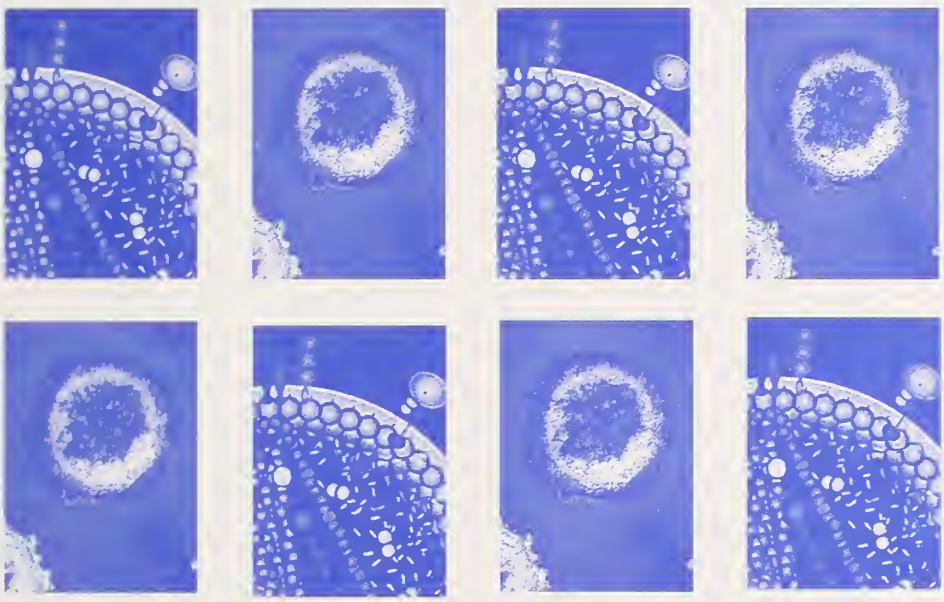
Objective:

6.B **Establish appropriate infrastructure for the conduct of HIV research nationally and internationally.**

Strategies:

- Enhance and improve research capacity and infrastructure with particular emphasis on AIDS-related intervention research such as vaccines, mother-to-child interventions, behavioral interventions, OIs, STDs, microbicides, and clinical trials methodologies;
- Ensure adequate facilities and resources to study AIDS-related animal models;
- Provide expanded funding for pilot animal model studies at primate centers and other facilities;
- Continue the Research Facilities Infrastructure Program (RFIP) and GCRC Program;
- Increase support for and awareness of the Biomedical Technology Resources program for structural studies of viral and host proteins;
- Provide for the long-term support of advanced in-country research and research infrastructure in those developing countries participating in priority AIDS-related intervention research such as methods to interrupt vertical, sexual, or parenteral transmission and efficacy trials of candidate HIV vaccines;
- Establish and support repositories for, and ensure access by qualified scientists to, samples (i.e., serum, PBMC, plasma, derived cell lines, CSF, biopsy, autopsy, and other key patient samples) and HIV strains from clinical trials, and natural history and epidemiological studies, especially in complex study settings (e.g., mother-infant transmission studies);

- Improve (and adequately disseminate) the process of requesting, prioritizing, and receiving laboratory samples so that access is as timely and equitable as possible;
- Promote Internet connections and availability at health sciences centers and hospitals for HIV-related research and patient care; and
- Promote research in and application of medical informatics (i.e., high-performance computing) for HIV/AIDS research and clinical practice.



Information Dissemination

AREA OF EMPHASIS:

Information Dissemination

Status:

The need for effective information dissemination approaches is integral to HIV prevention and treatment efforts. While the need for innovative and effective information approaches, including theory-based, testable approaches, has existed throughout the AIDS epidemic, it has been underscored in recent years by AIDS-related developments such as adherence issues related to the advent of new combination antiretroviral therapies and the reemergence of *Mycobacterium tuberculosis*, especially among HIV-infected individuals. The increasing numbers of HIV infection in population groups, such as women and adolescents, also underscore the need to disseminate HIV research findings and other related information efficiently and effectively.

The rapidly expanding field of information technology coupled with communications and information science research provides unprecedented opportunities to enhance the capabilities of individuals, organizations, and communities to address HIV and AIDS in the diverse ethnic, racial, age, and cultural groups they serve. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research into practice and to shape future research directions.

Consistent with this philosophy, OAR established a new NIH Information Dissemination Coordinating Committee in FY 1996. This Committee is charged with providing planning direction and assisting OAR and NIH in identifying and facilitating HIV/AIDS-related information dissemination activities, especially those that are trans-NIH. With the input of this Committee and the NIH ICDs, this section of the FY 1999 NIH Plan for HIV-Related Research reports on key activities and provides planning priorities and direction for the area of information dissemination.

Assessing and Responding to Information Needs

NIH recognizes that it is critical to establish relationships with target audiences that encourage and foster bidirectional communication. In this regard, NIH works with members of these audiences to understand their information needs, to involve them in developing strategies for information access and dissemination, and to involve them with the development of treatment and prevention guidelines as well as specific informational materials.

A major effort to enhance understanding of information needs, resources, and services began in June 1993 when NLM and OAR cosponsored a conference that brought together users of NIH information resources, including health care providers, scientists, information specialists, journalists, and members of the community affected by HIV/AIDS. The purpose of the conference

was to review the various HIV/AIDS information services, assess current efforts with respect to needs, and identify additional needs. The resultant recommendations were widely circulated and continue to be utilized for planning and informational purposes.

In response to recommendations from the conference, beginning in FY 1994, NLM has made awards of up to $35,000 each on an annual basis to enable community-based organizations and public and health science libraries to design their own programs for improving AIDS information access to targeted groups within their communities. Such groups include people with HIV/AIDS and the affected community as well as their care givers and the general public. Supported activities include purchasing equipment and telecommunications services, implementing Internet access, training in the use of sophisticated information tools, and developing language and culturally specific materials. NLM has also funded three major innovative efforts for improving HIV/AIDS information access: one to examine the functioning of a multitype consortium of academic, public, and hospital libraries along with community organizations as a means to get information to the affected community; a second to develop and field-test a training curriculum on accessing HIV/AIDS information by nonhealth professionals; and a third that provides access through a dedicated center in a public library.

An important challenge to NIH is to provide accurate and up-to-date HIV/AIDS treatment information to people in underserved communities and communities of color. A collaborative workshop held in 1993 provided insights about barriers to effective communication and recommended solutions that are being implemented by individuals and organizations at every level. The workshop was organized by NIAID working with OAR, the Health Resources and Services Administration, and the Public Education Technology Transfer Working Group of the NIAID ACTG.

As part of a larger program of training in the use of on-line databases that NLM has been conducting with the Historically Black Colleges and Universities (HBCUs), a new AIDS module has been created. The first pilot training course was taught in 1995 with materials specifically tailored for minority health professionals. Training in the use of electronic resources, based on curriculum developed as a result of this pilot course, continues at the HBCUs and through other groups of minority health professionals such as the National Association for Equal Opportunity in Higher Education (NAFEO).

NIAID is also working to increase understanding of clinical research and the differences between clinical trials and patient care, particularly by those in underserved communities. This communications effort is essential to NIAID's long-standing goal of recruiting hard-to-reach populations into clinical trials. A key part of this effort is building trust and strengthening outreach to local and national community organizations. Toward this end, NIAID has developed a kit

of English and Spanish language materials to assist health care providers, particularly in community clinics, in educating their patients about HIV and the diseases associated with AIDS and how to find out about clinical trials. The kit contains fact sheets on OIs and a "How To Help Yourself" series of eight attractive brochures for low-literacy audiences. These materials are available in bulk from the National AIDS Clearinghouse.

In December 1995, NIAID prepared and widely disseminated an updated NIAID HIV/AIDS Research Agenda. The document describes the breadth and depth of the comprehensive NIAID AIDS research program and future plans in those fields relevant to the NIAID mission. The document serves to inform others about the scope of NIAID's HIV/AIDS program.

After NIDA conducted a series of meetings with representatives of ethnic minorities and other underserved populations, the Institute began to develop drug abuse and HIV/AIDS-related materials.

NIDA's resulting drug abuse and AIDS public education program have provided specifically targeted television, radio, and print materials aimed at audiences at high risk for contracting or transmitting HIV infection. The first campaign, "Stop Shooting Up AIDS," targeted IDUs, their sexual partners, and others close to them. The target audience of the second campaign, entitled "AIDS, Another Way Drugs Can Kill," was the population ages 12 to 18 years. The third campaign, "Get High, Get Stupid, Get AIDS," was launched in August 1992 and targeted young adults ages 18 to 24 years. These campaigns pointed out the link between drug/alcohol abuse, altered judgment, and risky sexual behavior that can contribute to exposure to HIV. The messages were based on a growing body of research that demonstrated the association between drug/alcohol abuse and high-risk behaviors in these groups.

NIDA has developed material for general populations on the relationship between drug abuse and AIDS. For teens and young adults, NIDA produced two prevention pamphlets, "How Getting High Can Get You AIDS" and "How Not To Get High, Get Stupid, Get AIDS."

NIDA also supports other channels of information dissemination. NIDA's Community-Based HIV Prevention Research programs provide mechanisms whereby information can be rapidly shared between research staff, research participants, and their respective communities. The Community Epidemiology Work Group is a forum for U.S. and international agencies to present and discuss emerging drug-abuse trends and correlates, especially HIV/AIDS. This information is then distributed to prevention, treatment, and public health agency representatives, researchers, and policymakers.

Early in the AIDS epidemic when the risk of transfusion-transmitted HIV was still significant, the NHLBI instituted the National Blood Resources Education Program (NBREP). This program

facilitated the education of health care professionals about the proper use of blood and blood products in an effort to limit the use of potentially infected blood. The NBREP resulted in the publication and dissemination of multiple education pamphlets and articles in peer-reviewed medical journals.

In 1995, NIMH established a Consortium on Technology Transfer, supported by discretionary funds from OAR, Office of the Director, NIH. This consortium has developed and is testing different models of transferring HIV prevention technology from research settings to service settings and from service settings to researchers. This consortium is assessing the benefits of translating research findings on effective strategies for HIV prevention for community-based providers, funding agencies, health planners, and policymakers. Areas of focus include (1) increased use of methods of behavior change whose effectiveness has been empirically demonstrated; (2) increased capacity to identify and provide outreach to hard-to-reach populations; (3) increased use of more sophisticated and rigorous evaluation designs and methods; and (4) increased coordination of individual prevention methods in comprehensive communitywide strategies to change norms. Ultimately, these studies will be summarized and provided to service providers and policymakers as guidelines for HIV prevention dissemination.

In 1996, NIMH and the Office of Medical Applications of Research (OMAR) sponsored "The Consensus Development Conference on Interventions to Prevent HIV Risk Behaviors." The goal of OMAR consensus conferences was to review an area of NIH-supported research where there may be a gap between research accomplishments and clinical care. After careful review of the research, a statement was developed and circulated widely to policy- and health-related communities to inform them of the panel's consensus recommendations with respect to HIV prevention programs.

Clinical and Community Alerts

Since 1991, NIH has used a dedicated system of electronic and print notification, collectively known as Clinical Alerts, to disseminate rapidly to health care professionals, the news media, and to the general public information that critically affects the care of patients, such as results of HIV-related clinical trials. This mechanism was recommended by participants, including researchers, medical journal editors, and others, in a workshop convened by NIH to discuss expedited information dissemination. While affirming that traditional systems of reporting research results should be maintained, the group recognized that, in some exceptional circumstances, information with immediate clinical relevancy should be expeditiously reviewed and widely distributed prior to publication in a peer-reviewed medical journal. Clinical Alerts are available on-line on the MEDLARS system and provided for dissemination in academic health science centers and more than 3,000 hospitals; they are also transmitted via Internet to all

requestors. The National Network of Libraries of Medicine has developed methods to ensure the wide dissemination of the Clinical Alerts.

In February 1994, NIAID/NICHD utilized Clinical Alerts to disseminate rapidly the results of ACTG 076, which showed decreased transmission of HIV from mother to child when the mother and child received treatment with ZDV. A summary of the results was prepared by NIAID and made available on-line through all Clinical Alerts dissemination mechanisms. In addition, NIH staff played an integral role in the NICHD-chaired Public Health Service (PHS) Task Force that developed the clinical recommendations based on ACTG 076.

Physicians and patients must have access not only to Clinical Alerts and the results of clinical trials but also to clinical care guidelines, standards of care, and results of state-of-the-art meetings that redefine clinical care guidelines. Recommendations from the NIAID-sponsored state-of-the-art meeting on antiretroviral therapy for HIV-infected adults, held in June 1993, were widely distributed to the AIDS community and to health care providers. In addition, guidelines on OI prophylaxis, PCP prophylaxis for children with HIV, and recommendations for the use of ZDV to prevent perinatal HIV transmission, which have been developed by NIH and other agencies of the PHS, have been made available on-line in their complete versions as well as through an NIH-supported toll-free service. The "Report of the NIH Panel To Define Principles of Therapy of HIV Infection" and the "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents" will be disseminated through a number of information channels (by print distribution, electronically, and through toll-free information services) in early FY 1998.

It is also critical to ensure that prevention information is effectively disseminated to community service providers. NIDA has issued a series of Community Alerts to reach the drug-abuse-related HIV/AIDS community on emerging issues of concern, and has utilized its newsletter, *NIDA Notes,* to disseminate AIDS research information among drug-abusing populations and their service providers. NIDA has also produced an educational videotape for policymakers and professionals working in the drug abuse and HIV/AIDS fields. NIDA produced three Research Monographs in 1994–1995 to keep scientists and practitioners aware of recent developments in research methodologies and prevention approaches.

NICHD provided financial and technical assistance to the Agency for Health Care Policy and Research to develop its educational materials for pregnant, HIV-infected women. These materials provide information on using ZDV during pregnancy to reduce perinatal transmission of HIV and are intended to assist pregnant, HIV-infected women in deciding whether to use ZDV. The materials consist of a poster, brochures, and handouts, as well as audio and video tapes in several different languages.

Electronic Information Resources

Existing computerized databases including those on the MEDLARS system (AIDSLINE, AIDSTRIALS, AIDSDRUGS, and DIRLINE), as well as the AIDS Clinical Trials Information Service (ACTIS) and the HIV/AIDS Treatment Information Service (ATIS), are vital to information dissemination. They provide the foundation for the global dissemination of information concerning basic research, clinical trials availability and results, and standards of care as well as information of interest to HIV-infected individuals and their advocates.

Information available from the MEDLARS databases includes citations (with abstracts when available) to journal articles, books, and audiovisuals as well as abstracts from many major AIDS-related meetings and conferences (AIDSLINE); descriptions of clinical trials related to HIV, AIDS, and AIDS-related opportunistic diseases and the agents that are being studied in those trials (AIDSTRIALS/AIDSDRUGS); and international, national, and State organizations working in the AIDS area (DIRLINE). In response to recommendations by the AIDS advocacy community, the databases are available free of charge to users. The NLM has expanded the AIDSLINE database with the addition of abstracts from many scientific meetings. OAR has worked with NLM to identify meetings, particularly those meetings supported by NIH, and obtain copies of the abstracts for inclusion in the database. For example, the abstracts from the 4th Conference on Retroviruses and Opportunistic Infections, held in January of 1997, are available online through this mechanism. In addition, citations, with brief summaries, to substantive articles from more than 20 newsletters are being added to the database.

Initiated in 1989, ACTIS is a centralized resource providing information on NIH- and industry-sponsored clinical trials for HIV/AIDS. This is a free service to users and is jointly sponsored by NIAID, NLM, and FDA in collaboration with CDC. By dialing toll-free, 1-800-TRIALS-A, callers can speak to trained health specialists who access a database featuring information on AIDS clinical trials. Spanish-speaking specialists are available. The information can also be accessed directly through the NLM's AIDSTRIALS and AIDSDRUGS databases. This information is also available electronically from NLM as part of the Health Services and Technology Assessment Text (HSTAT) database which includes clinical practice guidelines and recommendations on many health concerns.

To complement the ACTIS project, NIH collaborated with other agencies of the PHS in the development of ATIS, which provides timely, accurate treatment information on HIV and AIDS through the CDC National AIDS Clearinghouse. Available since November 1, 1994, ATIS is a toll-free (1-800-HIV-0440), bilingual, telephone reference service for people with HIV disease, their families and friends, and health care providers, providing answers to questions about treatment of HIV infection as well as copies of federally approved

HIV/AIDS treatment guidelines and information.

The Internet is an expanding and increasingly important medium for information dissemination. NIH is increasingly utilizing this medium in tandem with its other information dissemination avenues. For example, NIH Home Pages such as those for NIAID (http://www.niaid.nih.gov/) and OAR (http://www.nih.gov/od/oar) are online, providing extensive HIV/AIDS research and programmatic information for the public, patients, health care providers, scientific investigators, and policymakers. ACTIS (http://www.actis.org/) and ATIS (http://www.hivatis.org/) both have World Wide Web sites that will increase their usefulness. NLM has created a World Wide Web Home Page specifically for HIV/AIDS-related information (http://sis.nlm.nih.gov/aidswww.htm). This serves as an entry point to many of the HIV/AIDS-related resources available from NIH as well as those from NLM. It also serves as a guide to selected resources worldwide.

NIDA is establishing a telephone- and fax-based information system to provide the public with critical information on all aspects of drug abuse and drug-abuse-related HIV/AIDS. Information on these services will be available through the NIDA Home Page (http://www.nida.nih.gov).

Improved Coordination

NIH has called for leadership at the PHS level for coordination of activities related to defining standard HIV information needs and related responsibilities. A special interagency working group for HIV/AIDS information dissemination has been formed under the DHHS Office of HIV/AIDS Policy. The working group provides a forum for the coordination of HIV/AIDS information and the formation of policy recommendations on related issues.

A "Guide to NIH HIV/AIDS Information Services," developed by NLM and OAR, has been updated annually and made available in both printed and electronic format through NLM's AIDS Home Page (http://sis.nlm.nih.gov). This pamphlet provides a comprehensive listing of NIH-supported information services that assist care and service providers, patients, and the public in their quest for knowledge about HIV/AIDS. This pamphlet describes these services as well as selected information services sponsored by other agencies of the PHS. The electronic version provides links to all NIH and PHS sites and resources that are described in the pamphlet.

NIH strives to disseminate information in a manner that is useful to health care providers, service providers, people with HIV/AIDS and their advocates, at-risk populations, and basic and applied researchers. It is therefore important to further understand and improve all aspects of information dissemination and communication processes. Of particular importance is understanding and improving the information exchange process, especially with respect to identifying and overcoming barriers to effective communication.

Additionally, research is needed to evaluate the effectiveness of information and behavior change communication campaigns.

NIH recognizes the critical importance of disseminating internationally research and treatment information, patient management guidelines, and research results that have an impact on the care of HIV-infected individuals in diverse international settings. The existing computerized databases from NLM as well as from ATIS and ACTIS are available worldwide. However, a number of special issues remain, including the lack of computer capabilities and access to journals in many countries, language barriers between the United States and other countries (as well as dialect and cultural barriers within countries), and the lack of resources to provide a standard of care comparable with that available in the United States.

Effective and efficient information dissemination and exchange are important tools in the effort to control and end the AIDS epidemic. NIH has responsibility for disseminating information to support research, treatment, and prevention related to HIV and AIDS. Progress in these areas depends upon the transfer of information to researchers, health care providers, those who provide HIV-related services, and HIV-infected individuals and their advocates. These audiences have varying needs for information that is critical in the fight against HIV/AIDS. Three scientific issues are presented here, each relating to the others, each an NIH priority in FY 1999.

Scientific Issue:

Effective Communication: Exchange of information about basic, clinical, and behavioral HIV/AIDS research findings is essential to progress in research and ultimately to improved care and treatment for HIV-infected people. The traditional methods of reporting ongoing studies and research results in peer-reviewed journals and at scientific meetings reach only a limited audience. Health educators, health care providers, patients, and other constituents of the NIH need to know the results of clinical and prevention intervention studies, state-of-the-art recommendations, and the most up-to-date standards of health care. As the epidemic has spread to new and hard-to-reach populations, special information outreach efforts need to be made to provide critical information to affected populations and their service providers. This information should be timely, include discussion of the potential implications of research findings for patient care, and should be in a form that audiences can use. The latest computer and information technologies should be exploited whenever appropriate. The findings resulting from communications research should be incorporated into the strategies to carry out this objective.

Objective:

7.A **Support the effective dissemination, communication, and utilization of HIV/AIDS information to all constituent communities of the NIH.**

Strategies:

- Rapidly disseminate new research findings with information on their potential implications on prevention, care, and treatment of HIV-infected individuals;
- Utilize cutting-edge computer and other information dissemination technology (including the World Wide Web) to disseminate up-to-date HIV/AIDS information;
- Expand access to current treatment and patient management guidelines including state-of-the-art care and information on clinical trials using multiple technologies

such as, but not limited to, on-line access (AIDSTRIALS and AIDSDRUGS databases and HSTAT) and voice access (ATIS and the ACTIS);

- Improve current techniques and develop and evaluate new techniques for the two-way communication of information to scientific and lay audiences, particularly to hard-to-reach populations;
- Improve outreach and support access to HIV/AIDS information resources by community groups, health care providers, and community-based HIV/AIDS service organizations;
- Enhance understanding of HIV and basic and clinical research processes by health care providers, community-based HIV/AIDS service organizations, social service organizations, policymakers, and persons with HIV/AIDS through developing and disseminating educational information;
- Develop mechanisms for rapidly disseminating information on research in progress to the research community in order to increase collaboration, reduce duplication of effort, and enhance the discovery process;
- Promote and enhance the exchange of scientific information and communication between public and private research enterprises, such as enhancing communication with the pharmaceutical industry concerning research on the development of therapeutics and vaccines and working with industrial scientists to make information concerning HIV protein structures available to the general scientific community;
- Communicate and exchange information internationally on topics such as prevention and treatment, patient management guidelines, and research results that improve the care of HIV-infected individuals, including those in developing countries;
- Support the exchange of basic and applied research information at community, regional, national, and international conferences and workshops;
- Provide on-line (in advance when possible) the full text of abstracts and other information from scientific meetings;
- Collect, archive, and promote use of existing data from NIH-supported basic and applied research for secondary data analysis;
- Widely disseminate information concerning specimen repositories (including existing repositories), specimens available, and relevant information concerning cohorts, contact people, and the process for obtaining access to samples;

- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members and information dissemination intermediaries; and
- Widely disseminate the annual update of the NIH Plan for HIV-Related Research and other HIV-related reports as they become available.

Scientific Issue:

Research: In light of the changing HIV/AIDS epidemic, assessments are needed to identify the important information needs of and barriers for relevant target audiences such as health care providers, service providers, people with HIV and their advocates, at-risk populations, basic and applied researchers, and the general public. Although significant communication efforts have been initiated, some communities still may not be (1) receiving needed information, (2) receiving information in a context appropriate for the audience, (3) comprehending the information, or (4) translating the information into action. New approaches are needed to ensure that the communication of information resulting from HIV/AIDS research is optimally effective.

Objective:

7.B **Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant target audiences.**

Strategies:

- Assess the information needs of, and sources of information used by, various audiences, including biomedical and behavioral research communities, health care providers, service providers, people with HIV and their advocates, at-risk populations, and the general public;
- Identify obstacles to information dissemination; develop and test possible ways to overcome these obstacles;
- Develop, test, and evaluate innovative strategies for effectively reaching specific audiences (e.g., adolescents, drug users, and other hard-to-reach populations) with relevant HIV information;

- Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV behavior-change interventions and clinical practices; and
- Evaluate the effectiveness of new technologies for disseminating basic and applied research findings.

Scientific Issue:

Coordination: The scientific and lay communities look to the NIH as a central source of information on HIV/AIDS. Since multiple NIH ICDs disseminate HIV/AIDS information to these communities, coordination of efforts is essential. In order to make more effective use of limited Federal dollars, increase efficiency, make better use of new technologies, and ensure credibility with the scientific and lay communities, NIH must demonstrate ongoing collaboration and coordination of communication activities within the NIH and between the NIH and other Federal agencies, public health departments, private companies, international groups, other granting agencies, community groups, and universities.

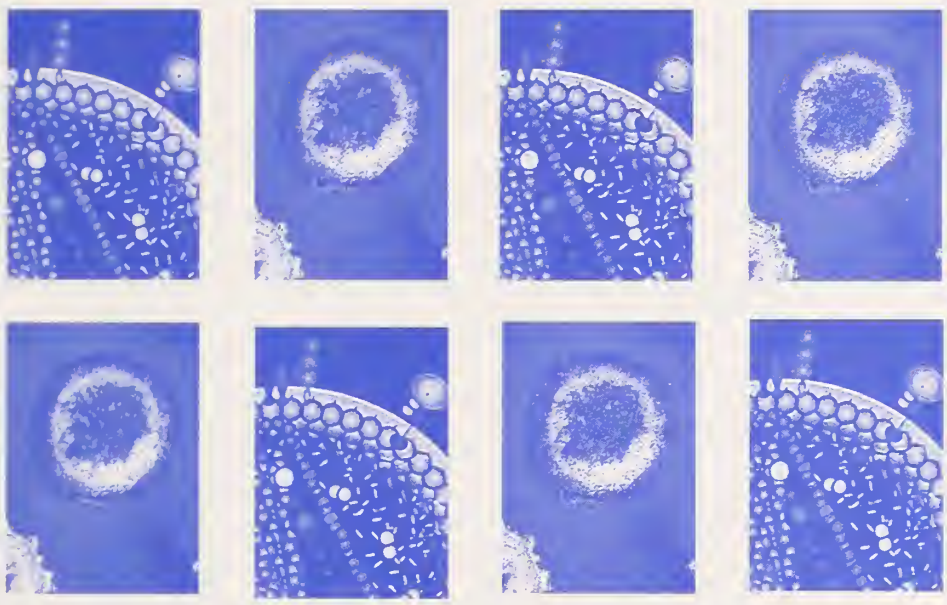
Objective:

7.C **Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communications activities among NIH ICDs and with other Federal and non-Federal groups.**

Strategies:

- Build ongoing partnerships between community-based organizations and basic, clinical, and behavioral researchers to encourage exchange of information and experience;
- Enhance research, treatment, and prevention efforts through requirements in appropriate funding proposals to establish communication and coordination;
- Support the NIH OAR Information Dissemination Coordinating Committee to promote and foster information dissemination, research, and programmatic efforts across the ICDs and between U.S. Government agencies;
- Promote closer interagency collaboration within the DHHS Coordinating Committee on HIV/AIDS on information dissemination programs;
- Coordinate collaboration among all ICDs in the provision of information about their clinical trials for HIV/AIDS to the ACTIS;

- Maintain an interface with the Cancer Information Service and Physician Data Query (PDQ) database to provide information on clinical trials for AIDS-related malignancies;
- Expand the development and use of HIV/AIDS resources on the Internet to facilitate national and international research collaboration and data sharing;
- Continue collaborations with UNAIDS, the Pan American Health Organization (PAHO), and international AIDS agencies or societies on information/ communications efforts, including information about international clinical trials;
- Collaborate with public and health sciences libraries, health care providers, and community-based HIV/AIDS service organizations to facilitate access to needed information;
- Work within DHHS, including the Health Care Financing Administration (HCFA), and with the private sector in the development of medical standards of care for determining guidelines for reimbursement;
- Collaborate with other PHS agencies in the development of training regarding HIV prevention, treatment, research, and education for health care providers, AIDS service providers, and health educators; and
- Expand the inclusion of academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.



Appendix A

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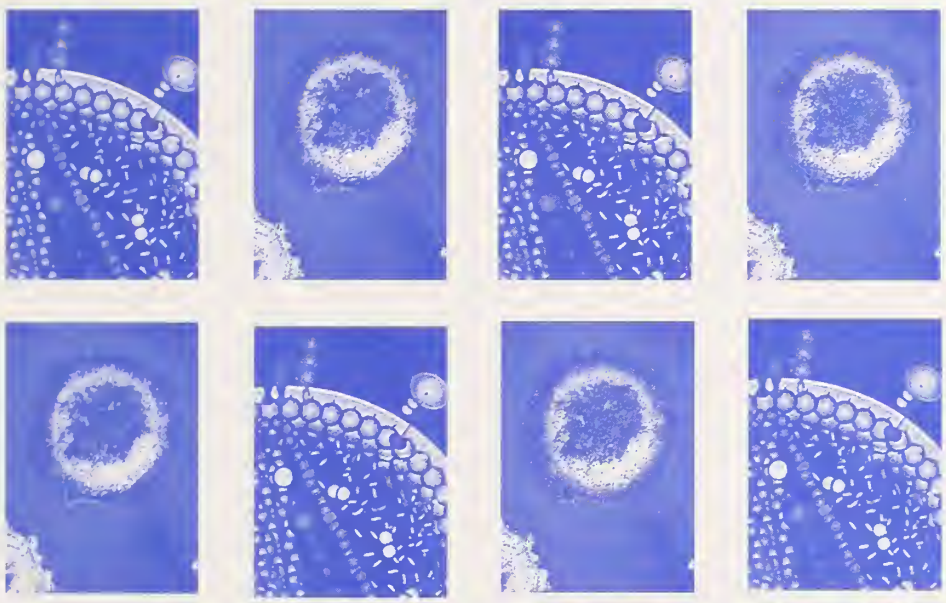

Appendix B

APPENDIX B

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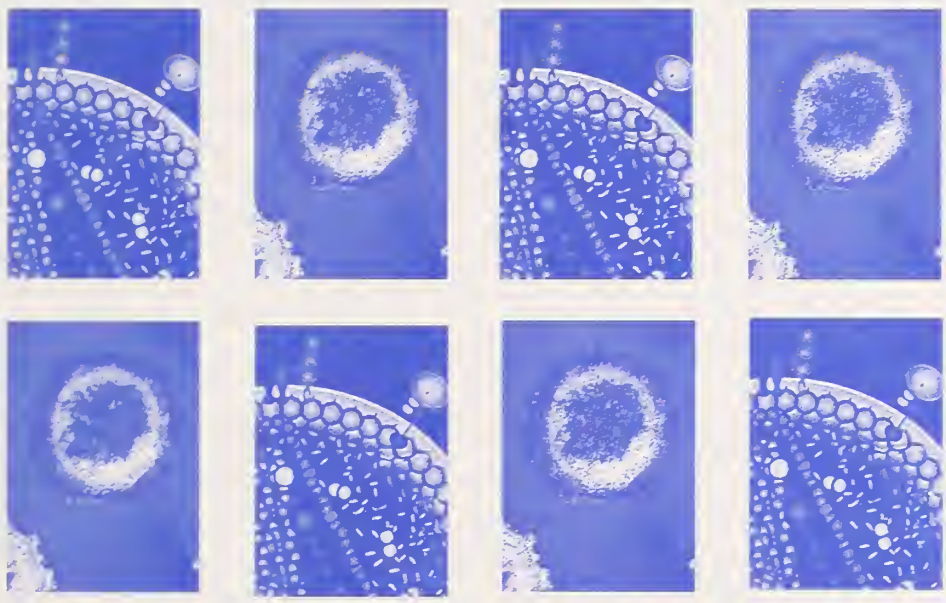

Appendix C

APPENDIX C

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